MELANOCORTIN RECEPTOR 4 (MC4) AGONISTS AND THEIR USES

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The present invention relates to peptide agonists of the MC4 receptor, and as such are useful in the treatment of disorders responsive to the activation of this receptor, such as obesity, diabetes mellitus and male and/or female sexual dysfunction.
MELANOCORTIN RECEPTOR 4 (MC4) AGONISTS AND THEIR USES

[0001] The present invention relates to peptide agonists of the MC4 receptor and as such are useful in the treatment of disorders responsive to the activation of this receptor, such as obesity, diabetes mellitus, and male and/or female sexual dysfunction.

[0002] The proopiomelanocortin (POMC) gene encodes a 31-36 kDa pre-prohormone, from which seven mature peptide hormones are derived. POMC processing occurs in a tissue specific manner yielding four distinct melanocortin peptides: adrenocorticotropic hormone (ACTH), α-melanocyte stimulating hormone (α-MSH), β-MSH, and γ-MSH.

[0003] Five melanocortin receptors have thus far been identified and are referred to herein as MC1, MC2, MC3, MC4, and MC5. MC1, whose primary endogenous ligand is α-MSH, is associated with pigmentation. MC2, whose primary endogenous ligand is ACTH, is associated with steroidogenesis. MC2 is distinctly different from the other melanocortin receptors and is not expected to interact with endogenous or synthetic MSHs other than ACTH or analogues thereof (Schöth et al., Life Sciences 59(10):797-801, 1996). MC5 is believed to have two primary ligands, α-MSH and ACTH, and is associated with exocrine and sebaceous gland lipid secretion.

[0004] Diverse lines of evidence, including genetic and pharmacological data obtained in rodents and humans, support a role for the MC4 receptor in the regulation of energy homeostasis, specifically regulating food intake and metabolism. The distribution of MC4 receptors in the brain correlates well with the areas in the brain which show high sensitivity to melanocortin-mediated feeding behavior (Maiden et al., Eur J. Pharmac. 440(2-3):141-57, 2002). In addition, the MC4 receptor is believed to be significantly involved in regulating body weight as evidenced by the fact that MC4r−/− mice are obese, and humans with mutations in the melanocortin MC4 receptor gene are obese. Thus, MC4 receptor agonists may be beneficial for the treatment of obesity.

[0005] The development of selective peptide agonists for melanocortin receptors has closely followed the identification of the various melanocortin receptor subtypes and their perceived primary ligands. Id. α-MSH, a 13-amino acid peptide, is a non-selective agonist at four melanocortin receptors, MC1 and MC3-MC5. NDP-α-MSH is a more potent, protease resistant, but still non-selective analogue of α-MSH.

[0006] The lactam derived from the N-10 fragment of NDP-α-MSH, known as MTII, is even more potent in vivo than NDP-α-MSH but is non-selective. Replacement of the D-Phe with D-(2)Na1 in MTII, yielded a high affinity antagonist for MC3 and MC4 that is an agonist for the MC1 and MC5 receptors. This peptide is known as SHU9119.

[0007] Although many peptides cyclized via disulfide bridges are MC4 receptor agonists, several are MC4 receptor antagonists with moderate selectivity over the MC3 receptor. The peptide HS014 is a partial agonist at the MC1 and MC5 receptors, while the peptide HS024 does not display agonist activity at the MC1 and MC3 receptors. In addition, PCT Publication No. WO 00/35952 discloses certain peptides cyclized via disulfide bridges having utility as MC4 agonists.

[0008] Despite the progress discussed above and elsewhere, there continues to be a need for MC4 agonists with pharmacologically desirable selectivity, potency and efficacy, for use as a pharmaceutical, in particular, for the treatment of obesity. Especially desired are MC4 agonists with a clinically desirable pharmacology and safety profile.

Obesity

[0009] Obesity, and especially upper body obesity, is a common and very serious public health problem in the United States and throughout the world. According to recent statistics, more than 25% of the United States population and 27% of the Canadian population are overweight. Kuczynski, Amer. J. of Clin. Nutr. 55:495S-502S, 1992; Reeder et al., Can. Med. Assn. J., 23:226-33, 1992. Upper body obesity is the strongest risk factor known for type II diabetes mellitus, and is a strong risk factor for cardiovascular disease and cancer as well. Recent estimates for the medical cost of obesity are $150,000,000,000 worldwide. The problem has become serious enough that the surgeon general has begun an initiative to combat the ever-increasing adiposity rampant in American society.

Male and/or Female Sexual Dysfunction

[0010] The MC4 receptor appears to play role in other physiological functions as well, namely controlling grooming behavior, erection, and blood pressure. "Female sexual dysfunction" encompasses, without limitation, conditions such as a lack of sexual desire and related arousal disorders, inhibited orgasm, lubrication difficulties, and vaginismus.

[0011] "Erectile dysfunction" is a disorder involving the failure of a male mammal to achieve erection, ejaculation, or both. Symptoms of erectile dysfunction include an inability to achieve or maintain an erection, ejaculatory failure, premature ejaculation, and inability to achieve an orgasm. An increase in erectile dysfunction is often associated with age and is generally caused by a physical disease or as a side effect of drug treatment. The term "impotence" is often times employed to describe this prevalent condition. Synthetic melanocortin receptor agonists have been found to initiate erections in men with psychogenic erectile dysfunction (Wessels et al., "Synthetic Melanotropic Peptide Initiates Erections in Men With Psychogenic Erectile Dysfunction: Double-Blind, Placebo Controlled Crossover Study", J. Urol., 160:389-93, 1998). Activation of melanocortin receptors of the brain appears to cause normal stimulation of sexual arousal. Evidence for the involvement of the MC4 receptor in male and/or female sexual dysfunction is detailed in WO 00/74670.

Diabetes

[0012] Diabetes is a disease in which a mammal’s ability to regulate glucose levels in the blood is impaired because the mammal has a reduced ability to convert glucose to glycogen for storage in muscle and liver cells. In Type I diabetes, this reduced ability to store glucose is caused by reduced insulin production. “Type II Diabetes” or “non-insulin dependent diabetes mellitus” (NIDDM) is a form of
diabetes which is due to a profound resistance to insulin stimulating or regulatory effect on glucose and lipid metabolism in the main insulin-sensitive tissues: muscle, liver, and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation, and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. When these cells become desensitized to insulin, the body tries to compensate by producing abnormally high levels of insulin, and hyperinsulinemia results. Hyperinsulinemia is associated with hypertension and elevated body weight. Since insulin is involved in promoting the cellular uptake of glucose, amino acids, and triglycerides from the blood by insulin sensitive cells, insulin insensitivity can result in elevated levels of triglycerides and LDL which are risk factors in cardiovascular diseases. The constellation of symptoms, which includes hyperinsulinemia, combined with hypertension, elevated body weight, elevated triglycerides and elevated LDL, is known as Syndrome X.

Applicants have discovered compounds that have an unexpectedly high affinity for the MC4 receptor and are selective for the MC4 receptor over other melanocortin receptor subtypes.

The present invention is directed to compounds represented by the following Structural Formula I (SEQ ID NO:199):
[0017] R² is —H, —NH₂, —NH(C(O)CH₃), —NH(C)(O)(CH₂)₂CH₃, —NH(Tyr(C(O)CH₃), R¹SO₂NH, Ac-Cya-NH, Tyr-NH, HO-(C₆H₅)-CH₃CH₂C(O)NH, or CH₃-(C₆H₅)-C(O)₂CH₂CH₂C(O)NH;

[0018] R³ is C₁-C₄ straight or branched alkyl, NH₂—CH₂—(CH₂)₅—, HO—CH₂—, (CH₂)₂CHNH(CH₂)₄—, R⁴(CH₂)₅—, R⁵SO₂NH, Ser, Ile,

[0019] q is 0, 1, 2, or 3;
[0020] R⁶ is a phenyl or C₆-C₁₄ bicyclic aryl;
[0021] m is 1 or 2;
[0022] n is 1, 2, 3, or 4;
[0023] R⁷ is (CH₂)ₚ or (CH₃)₂C—;
[0024] p is 1 or 2;
[0025] R¹⁰ is NH—or is absent;
[0026] R⁸ is a 5- or 6-membered heteroaryl or a 5- or 6-membered heteroaryl ring optionally substituted with R⁴;
[0027] R⁹ is H, C₁-C₄ straight or branched alkyl, phenyl, benzyl, or (C₆H₅)—CH₂—O—CH₂—;
[0028] R⁸ is phenyl, a phenyl ring optionally substituted with X, or cyclohexyl;
[0029] X is H, Cl, F, Br, methyl, or methoxy;
[0030] R¹¹ is —C(O) or —CH₂;
[0031] R¹² is —NH₂, —OH, glycine, NH₂-Pro-Ser-, NH₂-Pro-Lys-, HO-Ser-, HO-Pro-Ser-, HO-Lys-, -Ser alcohol, -Ser-Pro alcohol, -Lys-Pro alcohol, HOCH₂CH₂-O—CH₂CH₂NH, NH₂-Phe-Arg-, NH₂-Glu-, NH₂CH₂RCH₂NH, RHN—, or RO— where R is a C₁-C₄ straight or branched alkyl; and
[0032] L is —S—S—or —S—CH₂—S—.

[0033] In a preferred embodiment, the invention is directed to compounds represented by the following Structural Formula II (SEQ ID NO:200):
[0034] W is a single bond, Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr, Trp, or Phe;

[0035] R³ is —H, —C(O)CH₃, —C(O)(CH₂)ₙCH₃, —C(O)(CH₂)ₙNH—CH₂—NH—CH₂—NH—CH₂—H; Tyro-oxy-Tyr-Arg, Ac-Dab, Ac-Dap, N-succinyl-Tyr-Arg, N-propionyl, N-valeryl, N-glutaryl-Tyr-Arg, N-butyryl.

[0037] R³ is C₃₋C₄ straight or branched alkyl, Ser, Ile,

[0038] q is 0, 1, 2, or 3;

[0039] m is 1 or 2;

[0040] p is 1 or 2;

[0041] R⁴ is H or C₃₋C₄ straight or branched alkyl;

[0042] X is H, Cl, F, Br, methyl, or methoxy; and

[0043] R² is —NH₂, —OH, glycinol, -Ser-Pro-NH₂, -Lys-Pro-NH₂, -Ser-Pro-Arg, -Ser-Pro-Arg, -Lys-Pro-Arg, -Arg-Phe-NH₂, -Glu-NH₂, —NHR, or —OR, where R is a C₃₋C₄ straight or branched alkyl.

[0044] In another embodiment, the present invention is directed to compounds represented by Structural Formula II with the proviso that the combination of R₁, Tyr, R₂, Arg, W=Glu, R₃=H, X=H, m=1, p=1, and R₅=NH₂ is specifically excluded.

[0045] Another preferred embodiment of the present invention includes compounds of Structural Formula III (SEQ ID NO:201):
[0046] and pharmaceutically acceptable salts thereof, wherein

[0047] W is Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr, Trp, Phe, Lys, Leu, Cya, or is absent;

[0048] R₁ is —H, —C(O)CH₃, —C(O)(CH₂)₄CH₃, —C(O)(CH₂)₄NHCH(NH)NH₂, Tyr-β-Arg, Ac-Tyr-β-Arg, gluconoyl-Tyr-Arg, Ac-diaminobutyryl, Ac-D-amino propionyl, N-propionyl, N-butyryl, N-valeryl, N-methyl-Tyr-Arg, N-glutaryl-Tyr-Arg, N-succinyl-Tyr-Arg, R₁ = SO₂NHCC(CH₃)₂CH₂C(O)—, or R₁ = SO₂NHCC(CH₃)₂CH₂C(O)Arg;

[0049] R₂ is —H, —NH₂, —NHCO(CH₂)₄CH₃, —NH-C(O)(CH₂)₄CH₃, —NH-TyrC(O)CH₃, R₁SO₂NH—, Ac-Cya-NH—, Tyr-ΝH—, HO—(C₆H₅)—CH₂O—CH₂—;

[0050] R₃ is C₁-C₄ straight or branched alkyl, NH—, CH₂—(CH₂)₄—, R₂SO₂NH—, Ser, Ile,

TABLE 1

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[0066] A preferred embodiment of the invention includes Compound Nos. 48, 52, 132, 137, and 155. More preferred is a group consisting of Compound Numbers 52 and 137. Another more preferred embodiment includes Compound Number 137, denoted by the name Ac-cyclo[Cys-His-D-Phe-Arg-Trp-Cys]-NH₂. A most preferred embodiment of the present invention includes Compound Number 52, denoted by the name Ac-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂.

[0067] In one embodiment, the present invention relates to pharmaceutical compositions comprising at least one compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0068] In another embodiment, the present invention relates to a method for agonizing the MC₄ receptor, which comprises administering to a patient in need thereof an effective amount of a compound represented by Structural Formula 1, Structural Formula 2, or Structural Formula 3, or a pharmaceutical salt thereof.

[0069] In another embodiment, the present invention relates to a method of treating obesity in a mammal, comprising the step of administering to the mammal in need thereof a pharmaceutically effective amount of at least one compound of Structural Formula 1, Structural Formula 2, or Structural Formula 3, or a pharmaceutical salt thereof.

[0070] In another embodiment, the present invention relates to a method of treating diabetes mellitus in a mammal, comprising the step of administering to the mammal in
need thereof a pharmaceutically effective amount of at least one compound of Structural Formula I, Structural Formula II, or Structural Formula III, or a pharmaceutical salt thereof.

[0071] In another embodiment, the present invention relates to a method of treating male and/or female sexual dysfunction in a mammal, comprising the step of administering to the mammal in need thereof a pharmaceutically effective amount of at least one compound of Structural Formula I, Structural Formula II, or Structural Formula III, or a pharmaceutical salt thereof.

[0072] In another embodiment, the present invention is further related to the use of the compound of Structural Formula I, Structural Formula II, or Structural Formula III, or a pharmaceutical salt thereof, as a medicament.

[0073] In another embodiment, the present invention is further related to the use of the compound of Structural Formula I, Structural Formula II, or Structural Formula III, or a pharmaceutical salt thereof, in the manufacture of a medicament for treating obesity.

[0074] In another embodiment, the present invention is further related to the use of the compound of Structural Formula I, Structural Formula II, or Structural Formula III, or a pharmaceutical salt thereof, in the manufacture of a medicament for treating diabetes mellitus.

[0075] In another embodiment, the present invention is further related to the use of the compound of Structural Formula I, Structural Formula II, or Structural Formula III, or a pharmaceutical salt thereof, in the manufacture of a medicament for treating sexual dysfunction.

[0076] The compounds of the present invention also can be effective in treating and preventing diabetes mellitus, and male and female sexual dysfunction. In addition, the compounds can be associated with a more favorable safety profile than compounds currently used to treat these conditions.

[0077] The terms used to describe the instant invention have the following meanings herein.

[0078] When a compound represented by Structural Formula I, Structural Formula II, or Structural Formula III has more than one chiral substituent, it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art (for example, chromatography or crystallization), and the individual enantiomers within each pair may be separated using methods familiar to the skilled artisan. The present invention includes each diastereoisomer of compounds of Structural Formula I, Structural Formula II, and Structural Formula III, and mixtures thereof.

[0079] Certain compounds of Structural Formula I, Structural Formula II, and Structural Formula III may exist in different stable conformational forms, which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of Structural Formula I, Structural Formula II, and Structural Formula III, and mixtures thereof.

[0080] Certain compounds of Structural Formula I, Structural Formula II, and Structural Formula III may exist in zwitterionic form, and the present invention includes each zwitterionic form of compounds of Structural Formula I, Structural Formula II, or Structural Formula III, and mixtures thereof.

[0081] As used herein, “C₁₄-C₄ straight or branched alkyl” means a straight chained or branched hydrocarbon having 1 to 4 carbon atoms, which is completely saturated and unsubstituted. “C₅₋C₇ cycloalkyl” refers to a saturated, unsubstituted hydrocarbon ring having 3 to 7 carbon atoms. A “C₁₋C₄ straight or branched heteroalkyl” refers to a straight chained or branched hydrocarbon having 1 to 4 carbon atoms, which is completely saturated and unsubstituted, that also contains at least one “heteroatom.” A “heteroatom” is nitrogen, oxygen, or sulfur. “C₅₋C₇ heterocycloalkyl” refers to a saturated, unsubstituted hydrocarbon ring having 3 to 7 carbon atoms, which also contains at least one “heteroatom.” “C₁₋C₄ straight or branched alky1, C₃₋C₅ cycloalkyl, C₃₋C₅ straight or branched heteroalkyl, and C₅₋C₇ heterocycloalkyl” may be used as generic modifiers to describe a genus of substituents on another functional group such as a carbonyl, sulfonyl, or sulfonamide. For example, a “C₂₋C₅ cycloalkylcarbonyl” refers to a genus of saturated, unsubstituted hydrocarbon rings having 3 to 7 carbon atoms that are bonded to a carbonyl group.

[0082] A “C₃₋C₄ cyclic aryl” refers to two or three hydrocarbon rings fused together, having 8 to 14 carbon atoms, such as naphthalene. A C₃₋C₁₄ bicyclic aryl ring system has at least one aromatic ring. A “5- or 6-membered heteroary1” refers to a monocyclic aromatic ring having 5 or 6 atoms, of which 1-4 atoms are heteroatoms. An “8- to 14-membered bicyclic heteroary1” refers to two or three hydrocarbon rings fused together, having 8 to 14 atoms, at least one aromatic ring, and 1-4 heteroatoms.

[0083] A phenyl, benzyl, benzoyl, C₃₋C₁₄ bicyclic aryl, 5- or 6-membered heteroaryl, or 8- to 14-membered bicyclic heteroaryl may be unsubstituted or substituted with C₁₋C₄ straight or branched alky1, F, Cl, Br, —OH, methoxy, phenyl, benzyl, benzy1, or benzyloxyethyl. Furthermore, phenyl, benzyl, benzoyl, C₅₋C₁₄ bicyclic aryl, 5- or 6-membered heteroaryl, and 8- to 14-membered bicyclic heteroaryl may be used as generic modifiers to describe a genus of substituents on another functional group such as a carbonyl, sulfonyl, or sulfonamide. For example, a “C₅₋C₁₄ bicyclic arylsulfon1” refers to a genus of bicyclic aryl rings having 8 to 14 carbon atoms that are bonded to a sulfon1 group.

[0084] Modified amino acids are indicated by parentheses around the amino acid and the modification thereto (e.g., (4-Cl-D-Phe) is a 4-chloro modification on the D-isomer of phenylalanine). With respect to moieties depicted in Structural Formula I, Structural Formula II, and Structural Formula III, the single letter designations are as defined and do not refer to single letter amino acids corresponding to those letters.

[0085] The letter “D” preceding the above-mentioned 3-letter abbreviations, e.g., “D-Phe,” means the D-form of the amino acid. When the single letter abbreviation is used for an amino acid, a “d” will precede the letter to designate the D-form of the amino acid (e.g., dPhe).

[0086] An “amino alcohol” is an amino acid that has been modified by reducing the carbonyl group of the C-terminus to a methylene group. Amino alcohols are denoted by the
general nomenclature “Xaa alcohol,” wherein Xaa is the specific amino acid, from which the carbonyl group has been removed. To illustrate, “Ser alcohol” has the structure H₂N—CH(CH₃OH)—CH₂OH as opposed to the Ser amino acid structure of H₂N—CH(CH₂OH)—COOH.

0087 “Single bond,” as used herein, refers to a structure that does not contain an amino acid at the specified position. It is used to signify that an amino acid is absent from that position such that the carbonyl adjacent to that position on one side and the amine adjacent to that position on the other side form a peptide bond with each other.

0088 “*” means that both the D- and L-isomers are possible.

0089 “Ac” refers to acetyl (i.e., —C(O)CH₃).

0090 “Orn” refers to ornithine.

0091 “bCys” refers to homocysteine.

0092 “hArg” refers to homoarginine.

0093 “Lys(ipy)” refers to lysine(N-isopropyl).

0094 “Cit” refers to citrulline.

0095 “nLeu” refers to norleucine.

0096 “Me” refers to methyl.

0097 “Ome” refers to methoxy.

0098 “Cya” refers to cysteic acid.

0099 “Dap” refers to diaminopropionyl.

0100 “Dab” refers to diaminobutyryl.

0101 “MC4 agonist” refers to a compound that has affinity for the MC4 receptor and results in measurable biological activity in cells, tissues, and organs containing the MC4 receptor. Assays measuring such activity are well known in the art.

0102 The term “selective” means having an activation preference for a certain receptor over other receptors which can be quantified based on whole cell, tissue, or organism assays which demonstrate receptor activity. Selectivity is ascertained by comparison of EC₅₀ values at the relevant receptors referenced.

0103 “Pharmacologically-acceptable salt” refers to salts of the compounds of the Structural Formula I, Structural Formula II, or Structural Formula III that are substantially non-toxic to mammals. Typical pharmacologically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively. It should be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmaceutically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

0104 A pharmaceutical “acid addition salt” is a salt formed by reaction of the free base form of a compound of formula I with a pharmaceutical acid, such as described in the Encyclopedia of Pharmaceutical Technology, editors James Swarbrick and James C. Boylan, Vol. 13 (1996), “Preservation of Pharmaceutical Products to Salt Forms of Drugs and Absorption.” Specific salt forms include, but are not limited to the: acetate, benzoate, benzenesulfonate, 4-chlorobenzenesulfonate; citrate; ethanesulfonate; fumarate; d-glucuronate; d-glucuronate; glutarate; glycolate; hippurate; hydrochloride; 2-hydroxyethanesulfonate; dl-lactate; maleate; d-malate; l-malate; malonate; d-mandelate; l-mandelate; methanesulfonate; 1.5-naphthalenedisulfonate; 2-naphthalenesulfonate; phosphate; salicylate; succinate; sulfate; d-tartrate; l-tartrate; and p-toluenesulfonate.

0105 A pharmaceutical “base addition” salt is a salt formed by reaction of the free acid form of a compound of formula I with a pharmaceutical base, such as described in the Encyclopedia of Pharmaceutical Technology, supra. Specific salt forms include, but are not limited to the: calcium, diethanolamine, diethylamine, ethylenediamine, lysine, magnesium, piperazine, potassium, sodium, and tromethamine (Tris, Trizma) salts.

0106 The term “active ingredient” means the compounds generically described by Structural Formula I, Structural Formula II, or Structural Formula III, as well as the salts of such compounds.

0107 The term “pharmacologically acceptable” means that the carrier, diluent, excipients, and salt must be compatible with the other ingredients of the composition and not clinically deleterious to the recipient thereof. Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well-known and readily available ingredients.

0108 The terms “treating” and “treat”, as used herein, include their generally accepted meanings, i.e., alleviating, ameliorating, managing, preventing, prohibiting, restraining, slowing, stopping, or reversing the progression or severity of a pathological condition, or sequela thereof, described herein.

0109 The diseases, disorders or conditions for which compounds of the present invention are useful in treating include (1) obesity, (2) diabetes mellitus, and (3) male and/or female sexual dysfunction.

0110 “Preventing” refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein. The term “preventing” is particularly applicable to a patient that is susceptible to the particular pathological condition as determined by medical diagnosis.

0111 “Pharmacologically effective amount” means that amount of a compound, or salt thereof, that will elicit the biological or medical response of a tissue, system, or mammal and/or is capable of treating the conditions described herein, or that is capable of agonizing the MC3 and/or MC4 receptors. An “effective amount” of the peptide administered to a subject will also depend on the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. The recipient patient’s physician should determine the therapeutic dose administered in light of the relevant circumstances.

0112 A pharmaceutically effective amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount, when administered prophylactically to a patient, can also be
effective to prevent or lessen the severity of the mediated condition. The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts, in view of a variety of factors, including, without limitation, the route of administration, the prior medical history of the recipient, the pathological condition or symptom being treated, the severity of the condition/symptom being treated, and the age and sex of the recipient patient. However, it will be understood that the therapeutic dose administered will be determined by the attending physician in the light of the relevant circumstances.

Generally, an effective minimum daily dose of a compound of the present invention will exceed about 0.01 mg. Typically, an effective maximum daily dose will not exceed about 1000 mg. More preferably, an effective minimum daily dose will be between about 0.05 mg and 50 mg, more preferably between 0.1 mg and 10 mg. Most preferably, an effective minimum daily dose of an MC4R agonist peptide in the present invention will exceed about 2 μg/kg and will not exceed about 20 μg/kg. The exact dose may be determined, in accordance with the standard practice in the medical arts of “dose titrating” the recipient; that is, initially administering a low dose of the compound, and gradually increasing the dose until the desired therapeutic effect is observed. The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals.

A “mammal” is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes humans, monkeys, chimpanzees, gorillas, cattle, swine, sheep, dogs, cats, mice, and rats. The attending physician of ordinary skill can identify humans who will benefit from administration of the compounds and compositions of the present invention.

The term “patient” includes human and non-human animals such as companion animals (dogs and cats and the like), farm animals, and laboratory animals.

The term “pharmaceutical” when used herein as an adjective means substantially non-deleterious to the recipient patient.

A pharmaceutically effective amount of a compound of Structural Formula I, Structural Formula II, or Structural Formula III can be used for the preparation of a medicinal useful for treating weight loss, obesity, diabetes and male and female sexual dysfunction.

Formulation:

The present pharmaceutical compositions are prepared by known procedures using well-known and readily available ingredients. Such procedures may include, e.g., conventional mixing, dissolving, granulating, drug-making, levitating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Because compounds of the invention contain an acidic moiety (i.e., carboxy), the compounds of the invention may be formulated as a pharmaceutical base addition salt thereof; e.g., as the sodium salt. Similarly, because compounds of the invention contain a basic moiety (i.e., amino), the compounds can be formulated as a pharmaceutical acid addition salt, e.g., as the acetate salt.

In making the compositions of the present invention, the active ingredient (a compound of the present invention) will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier. When the carrier serves as a diluent, it may be a solid, semisolid, or liquid material that acts as a vehicle, excipient, or medium for the active ingredient. Thus, the compositions can be in the form of, e.g., a suspension, solution, or sterile injectable solution.

An injectable formulation, for example, a sterile injectable aqueous or oleaginous suspension, can be prepared using suitable dispersing or wetting agents and suspending agents. The sterile injectable formulation may be a solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, sterile water for injection (WFI), bacteriostatic water for injection (BWFI), Ringer’s solution, and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium. Fixed oils and fatty acids, such as oleic acid, may be employed in the preparation of an injectable formulation.

The compounds of the present invention, and the pharmaceutically acceptable salts, have valuable pharmacological properties and can be used in pharmaceutical compositions containing a pharmaceutically effective amount of a compound of the present invention, or pharmaceutically acceptable salts thereof, in combination with one or more pharmaceutically acceptable excipients. Excipients may include substances such as carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material, antimicrobial agents, and other conventional adjuvants. Proper formulation is dependent upon the route of administration chosen as well as any interactions between excipients. Pharmaceutical compositions typically contain from about 1 to about 99 weight percent of the active ingredient, which is a compound of the present invention.

Solid form formulations may include powders, tablets, and capsules. A solid carrier can be one or more substance that may also act as flavoring agents, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents, and encapsulating material.

Sterile liquid formulations may include suspensions, emulsions, syrups, and elixirs. The active ingredient may be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent. The injectable formulation may be sterilized, for example, by filtration through a bacteria- or virus-retaining filter, by radiation, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use.

The compounds of the present invention may be formulated in a unit dosage form prior to administration to the recipient patient. A “unit dosage form” is a physically discrete unit containing a unit dose, suitable for administration in human subjects or other mammals. For example, a unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A “unit dose” is a predetermined quantity of the active compound of the present invention, calculated
to produce the desired therapeutic effect, generally in association with one or more pharmaceutically acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.01 to about 1000 milligrams according to the particular treatment involved.

[0126] The compounds of the present invention can be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day, or by continuous infusion. Where delivery is via transdermal forms, of course, administration is continuous.

[0127] The compounds of the present invention can be administered by a variety of routes, including the oral, subcutaneous, topical, parenteral (e.g., intravenous and intramuscular), bronchial, or intranasal routes.

[0128] “Continuous infusion” of a compound of the present invention refers to controlled parenteral delivery of the peptide to a patient for an extended period of time. Administration via continuous infusion may be accomplished by, but is not limited to, delivery via pump, depot, suppository, pessary, transdermal patch or other topical administration (such as buccal, sublingual, spray, ointment, creme, or gel) using, for example, subcutaneous, intramuscular, intraperitoneal, intravenous, intracerebral, or intraarterial administration.

[0129] A pump delivering a compound of the present invention into the body may be implanted in the patient’s body. Alternatively, the patient may wear a pump externally, being attached to the patient’s body via catheter, needle, or some other connective means. Any pump that is suitable for the delivery of pharmaceuticals to a patient may be used. Examples include pumps such as those disclosed in U.S. Pat. No. 6,659,982.

[0130] A depot is a biocompatible polymer system containing a compound of the present invention and delivering the peptide over time. Examples include microspheres, microcapsules, nanoparticles, liposomes, a hydrogel, or other polymeric implants. Preferred periods for delivery of agonist by depot include one week, two weeks, and one month periods. If needed, another depot will be delivered to the patient for continued delivery of peptide.

[0131] Engineering a compound of the present invention to have a prolonged half-life will also result in continuous delivery of the MC4 receptor agonist to the receptor. Such modifications include conjugations with larger proteins such as albumin, antibody and antigen or chemical modifications that may increase half-life by linking fatty acids, polyethylene glycol (PEG) polymers, and other agents.

[0132] The compounds of the instant invention may be used effectively alone or in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage composition which contains a compound of Structural Formula I, Structural Formula II, or Structural Formula III, and one or more additional active agents, as well as administration of a compound of Structural Formula I, Structural Formula II, or Structural Formula III, and each active agent in its own separate pharmaceutical dosage formulation. Where separate dosage formulations are used, a compound of Structural Formula I, Structural Formula II, or Structural Formula III, and one or more additional active agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially; combination therapy is understood to include all of these regimens.

[0133] A preferred combination therapy for the treatment of obesity is the use of a compound of the present invention in combination with sibutramine (or active metabolites of sibutramine, e.g., desmethyl sibutramine and di-desmethyl sibutramine), preferably with sibutramine hydrochloride monohydrate. Another preferred combination is the use of a compound of the present invention in combination with orlistat.

[0134] A preferred combination therapy for the treatment of sexual dysfunction (erectile dysfunction) is the use of a compound of the present invention in combination with sildenafil citrate. Another preferred combination is the use of a compound of the present invention in combination with tadalafil. Yet another preferred combination is the use of a compound of the present invention in combination with vardenafil, preferably vardenafil hydrochloride.

[0135] The following examples are not intended to limit the invention in any way. All peptides of the present invention can be synthesized by solid-phase synthesis methods (Merrifield, J. Am. Chem. Soc. 85:2149-54, 1963) either by manual or automated synthesis techniques. The automated assembly can be carried out using either as ABI 431A or 433A synthesizer.

EXAMPLE 1

Synthesis of Compound No. 48: Ac-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH2

[0136] The sequence Arg-Cys-Glu-His-D-Phe-Arg-Trp-Cys is assembled by standard Fmoc chemistry utilizing an ABI 431 instrument, according to Scheme A outlined below. The automated assembly is carried out by using the standard Applied Biosystems single 1.5 hour dicyclohexylcarbodiimide/hydroxybenzotriazole (DCI/HOBT) activation protocol. The solid support utilized is Rink MBHA resin (Rink, Tet. Lett. 28:3787-90, 1987) and the side chain protecting group scheme is: Arg(Pbf), Cys(Trt), Glu(OtBu), Glu(Trt), His(Trt), Trp(Boc), Tyr(Bu). The protected amino acids and Rink resin can be purchased from Nova Biochem or Mid- west Biotech. Acetylation of the co-amino group, after the chain assembly, is carried out off-line with 5 equivalents acetic anhydride, 10 equivalents DIEA in dry DME or NMP, 1 h at room temperature. The finished peptide is simultaneously deprotected and cleaved from the resin using a scavenger cocktail of TFA/H2O/TIS/EDT (95/2/1/2, v/v/v), or TFA/H2O/TIS/anisole (92/2/4/2, v/v/v) 2 hours at room temperature. The solvents are then evaporated under vacuum, and the peptide is precipitated and washed three times with cold diethyl ether to remove the scavengers. The crude product is used directly in the cyclization reaction.

Cyclization Protocol

[0137] The oxidation of the free cysteine sulfhydryl groups is accomplished by either air oxidation in 0.2 M ammonium acetate buffer containing 20% dimethyl sulfoxide (DMSO) at pH 7.0, or by treatment with 2,2'-pyridylid- isulfide in 2.7 M guanidine buffer containing 50% DMSO. In each case, the final product is isolated by high performance liquid chromatography.
Purification

Purification is accomplished using standard preparative HPLC techniques. Immediately following the cyclization, the peptide is diluted and loaded onto an HPLC column and eluted with an aqueous 0.1% trifluoroacetic acid/acetonitrile gradient while monitoring at 214 nm. The appropriate fractions are pooled and lyophilized. Further characterization of the final product is performed using analytical HPLC and mass spectral analysis known in the art, and the data are summarized in Table 2 below.

Conversion to Acetate Salt

The peptide is adsorbed onto a 2.1×25 cm Zorbax C18 preparative column, which is equilibrated with 0.1% TFA/H2O. The column is then washed with 2 volumes of 0.1 M ammonium acetate/5% acetonitrile followed by 2 column volumes of water. The peptide is eluted using 2% acetic acid and lyophilized.
The following compounds are exemplified only for the purpose of illustration and should not be considered to limit the invention in any way.

EXAMPLE 2

Synthesis of Compound No. 1: Ac-cyclo[CYS-His-D-Phe-Arg-Trp-CYS]-NH₂

Can be prepared according to Example 1, with the exception that Fmoc-Glu(OTBu) and Fmoc-Arg(Pbf) in steps 6 and 8, respectively, are not used.

EXAMPLE 4

Synthesis of Compound No. 3: Ac-Tyr-Arg-cyclo
[Cys-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂

Can be prepared according to Example 1, with the exception that Fmoc-Ala is used instead of Fmoc-Glu(OTBu) in step 6. Fmoc-Tyr(Bu) is added between steps 8 and 9.

EXAMPLE 3

Synthesis of Compound No. 2: Ac-Cys-Arg-cyclo
[Cys-Ala-Ris-D-Phe-Arg-Trp-Cys]-NH₂

Can be prepared according to Example 1, with the exception that Fmoc-Glu(OTBu) in step 6 is replaced with Fmoc-Ala. Between steps 8 and 9, one extra step of Fmoc-Cya (Fmoc-cysteic acid) is added. In addition, peptide cyclization (forming the disulfide bond) is carried out on resin using 10 equivalents of iodine in DMF for 2 h at room temperature.

EXAMPLE 5

Synthesis of Compound No. 4: Ac-Tyr-Arg-cyclo
[Cys-Arg-His-D-Phe-Arg-Trp-Cys]-NH₂

Can be prepared according to Example 1, with the exception that Fmoc-Arg(Pbf) is used instead of Fmoc-Glu(OTBu) in step 6. Fmoc-Tyr(Bu) is used between steps 8 and 9.
EXAMPLE 6

Synthesis of Compound No. 5: Ac-Tyr-Arg-cyclo
[Cys-Asn-His-D-Phe-Arg-Trp-Cys]-NH₂

[0145] Can be prepared according to Example 1, with the exception that Fmoc-Asn is used instead of Fmoc-Glu(OrBu) in step 6. Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 7

Synthesis of Compound No. 6: Ac-cyclo[Cys-Asp-
His-D-Phe-Arg-Trp-Cys]-NH₂

[0146] Can be prepared according to Example 1, with the exception that Fmoc-Arg(Pbf) is not used in step 8. Fmoc-Asp is used instead of Fmoc-Glu(OrBu) in step 6.

EXAMPLE 8

Synthesis of Compound No. 7: Ac-Tyr-Arg-cyclo
[Cys-Asp-His-D-Phe-Arg-Trp-Cys]-NH₂

[0147] Can be prepared according to Example 1, with the exception that Fmoc-Asp is used instead of Fmoc-Glu(OrBu) in step 6. Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 9

Synthesis of Compound No. 8: Ac-cyclo[Cys-Gln-
His-D-Phe-Arg-Trp-Cys]-NH₂

[0148] Can be prepared according to Example 1, with the exception that Fmoc-Arg(Pbf) is not used in step 8. Fmoc-Gln is used instead of Fmoc-Glu(OrBu) in step 6.

EXAMPLE 10

Synthesis of Compound No. 9: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH

[0149] Can be prepared according to Example 1, with the exception that: Step 1 Fmoc-Cys(Trt) is not used; Fmoc-Glu(Trt) is used instead of Fmoc-Glu(OrBu) in step 6. In addition, preloaded Fmoc-Cys(Trt)-Wang resin (Wang, J. Am. Chem. Soc. 95:1328-33, 1972) is used instead of Rink resin.

EXAMPLE 11

Synthesis of Compound No. 10: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OMe

[0150] Can be prepared according to Example 10. After the cleavage, cyclization, and purification, the peptide (Compound No. 9) is dissolved in dry methanol. Then, hydrochloride gas is bubbled into the methanol solution for about half minute. The reaction is allowed to proceed at room temperature for ten minutes. The solvents are removed under vacuum, and the final product is purified as specified in Example 1.

EXAMPLE 12

Synthesis of Compound No. 11: Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-M-Cys]-NH₂

[0151] Can be prepared according to Example 1, with the exception that Fmoc-Gly is used instead of Fmoc-Glu(OrBu) in step 6. Fmoc-Tyr(tBu) is added after step 8. Acetylation with acetic anhydride in step 9 is omitted.

EXAMPLE 13

Synthesis of Compound No. 12: Ac-Tyr-Arg-cyclo
[Cys-Gly-His-D-Phe-Arg-Trp-Cys]-NH₂

[0152] Can be prepared according to Example 1, with the exception that Fmoc-Gly is used instead of Fmoc-Glu(OrBu) in step 6. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 14

Synthesis of Compound No. 13: Ac-Tyr-Arg-cyclo
[Cys-Ile-His-D-Phe-Arg-Trp-Cys]-NH₂

[0153] Can be prepared according to Example 1, with the exception that Fmoc-His is used instead of Fmoc-Glu(OrBu) in step 6. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 15

Synthesis of Compound No. 14: Ac-Tyr-Arg-cyclo
[Cys-Ile-His-D-Phe-Arg-Trp-Cys]-NH₂

[0154] Can be prepared according to Example 1, with the exception that Fmoc-Ile is used instead of Fmoc-Glu(OrBu) in step 6. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 16

Synthesis of Compound No. 15: Ac-cyclo[Cys-Leu-
His-D-Phe-Arg-Trp-Cys]-NH₂

[0155] Can be prepared according to Example 1, with the exception that Fmoc-Arg(Pbf) is not used in step 8. Fmoc-Leu is used instead of Fmoc-Glu(OrBu) in step 6.

EXAMPLE 17

Synthesis of Compound No. 16: Ac-cyclo[Cys-Lys-
His-D-Phe-Arg-Trp-Cys]-NH₂

[0156] Can be prepared according to Example 1, with the exception that Fmoc-Arg(Pbf) is not used in step 8. Fmoc-Lys(Boc) is used instead of Fmoc-Glu(OrBu) in step 6.

EXAMPLE 18

Synthesis of Compound No. 17: N-methyl-Tyr-Arg-
cyclo[Cys-Met-His-D-Phe-Arg-Trp-Cys]-NH₂

[0157] Can be prepared according to Example 1, with the exception that acetylation with acetic anhydride in step 9 is not used. Fmoc-N-methyl-Tyr is used after step 8. In addition, Fmoc-Met is used instead of Fmoc-Glu(OrBu) in step 6.

EXAMPLE 19

Synthesis of Compound No. 18: Ac-Tyr-Arg-cyclo
[Cys-Met-His-D-Phe-Arg-Trp-Cys]-NH₂

[0158] Can be prepared according to Example 1, with the exception that Fmoc-Met is used instead of Fmoc-Glu(OrBu) in step 6. Fmoc-Tyr(tBu) is used between steps 8 and 9.
EXAMPLE 20

Synthesis of Compound No. 19: Ac-Tyr-Arg-cyclo
[Cys-Phe-His-D-Phe-Are-Trp-Cys]-NH₂

[0159] Can be prepared according to Example 1, with the exception that Fmoc-Phe is used instead of Fmoc-Glu(OtBu) in step 6. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 21

Synthesis of Compound No. 20: Ac-Tyr-Arg-cyclo
[Cys- Pro-His-D-Phe-Arg-Trp-Cys]-NH₂

[0160] Can be prepared according to Example 1, with the exception that Fmoc-Pro is used instead of Fmoc-Glu(OtBu) in step 6. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 22

Synthesis of Compound No. 21: Ac-Tyr-Arg-cyclo
[Cys-Ser-His-D-Phe-Arg-Trp-Cys]-NH₂

[0161] Can be prepared according to Example 1, with the exception that Fmoc-Ser is used instead of Fmoc-Glu(OtBu) in step 6. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 23

Synthesis of Compound No. 22: Ac-Tyr-Arg-cyclo
[Cys-Thr-His-D-Phe-Arg-Trp-Cys]-NH₂

[0162] Can be prepared according to Example 1, with the exception that Fmoc-Thr is used instead of Fmoc-Glu(OtBu) in step 6. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 24

Synthesis of Compound No. 23: Ac-Tyr-Arg-cyclo
[Cys-Trp-His-D-Phe-Arg-Trp-Cys]-NH₂

[0163] Can be prepared according to Example 1, with the exception that Fmoc-Trp is used instead of Fmoc-Glu(OtBu) in step 6. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 25

Synthesis of Compound No. 24: Ac-Tyr-Arg-cyclo
[Cys-Tyr-His-D-Phe-Arg-Trp-Cys]-NH₂

[0164] Can be prepared according to Example 1, with the exception that Fmoc-Tyr(tBu) is used instead of Fmoc-Glu(OtBu) in step 6. Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 26

Synthesis of Compound No. 25: Ac-Tyr-Arg-cyclo
[Cys-Val-His-D-Phe-Arg-Trp-Cys]-NH₂

[0165] Can be prepared according to Example 1, with the exception that Fmoc-Val is used instead of Fmoc-Glu(OtBu) in step 6. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 27

Synthesis of Compound No. 26: Ac-Arg-cyclo[Cys-Cya-His-D-Phe-Arg-Trp-Cys]-NH₂

[0166] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6 is replaced with Fmoc-Cya. In addition, peptide cyclization (forming the disulfide bond) is carried out on resin using 10 equivalents of iodine in DMF at room temperature for 2 h.

EXAMPLE 28

Synthesis of Compound No. 27: Ac-D-Arg-cyclo
[Cys-Cya-His-D-Phe-Arg-Trp-Cys]-NH₂

[0167] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6 and Fmoc-D-Arg(Pbf) in step 8 are replaced with Fmoc-Cya and Fmoc-D-Arg(Pbf), respectively. In addition, peptide cyclization is carried out on resin using 10 equivalents of iodine in DMF at room temperature for 2 h.

EXAMPLE 29

Synthesis of Compound No. 28: Ac-Tyr-Arg-cyclo
[Cys-Cya-His-D-Phe-Arg-Trp-Cys]-NH₂

[0168] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6 is replaced with Fmoc-Cya. Fmoc-Tyr(tBu) is added between steps 8 and 9. In addition, peptide cyclization is carried out on resin using 10 equivalents of iodine in DMF for 2 h at room temperature.

EXAMPLE 30

Synthesis of Compound No. 29: cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0169] Can be prepared according to Example 1, with the exception that steps 8 and 9 are omitted.

EXAMPLE 31

Synthesis of Compound No. 30: Ac-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0170] Can be prepared according to Example 1, with the exception that Fmoc-Arg(Pbf) is not used in step 8.

EXAMPLE 32

Synthesis of Compound No. 31: Ac-cyclo[Cys-Glu-His-(4-F-D-Phe)-Arg-Trp-Cys]-NH₂

[0171] Can be prepared according to Example 1, with the exception that Fmoc-Arg(Pbf) in step 8 is not used. In addition, Fmoc-4-F-D-Phe is used in step 4 instead of Fmoc-D-Phe.

EXAMPLE 33

Synthesis of Compound No. 32: Ac-cyclo[Cys-Glu-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH₂

[0172] Can be prepared according to Example 1, with the exception that Fmoc-4-Cl-D-Phe is used in step 4 instead of Fmoc-D-Phe. Fmoc-Arg(Pbf) is not used in step 8.

EXAMPLE 34

Synthesis of Compound No. 33: Ac-cyclo[Cys-Glu-His-(4-Br-D-Phe)-Arg-Trp-Cys]-NH₂

[0173] Can be prepared according to Example 1, with the exception that Fmoc-Arg(Pbf) in step 8 is not used. In addition, Fmoc-4-Br-D-Phe is used instead of Fmoc-D-Phe.
EXAMPLE 35

Synthesis of Compound No. 34: Ac-cyclocys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys-NH₂

[0174] Can be prepared according to Example 1, with the exception that Fmoc-1-Me-His is used in step 5 instead of Fmoc-His(Trt). Fmoc-Arg(Pbf) in step 8 is omitted.

EXAMPLE 36

Synthesis of Compound No. 35: Ac-cyclocys-Glu-His-D-Phe-Arg-Trp-Cys-Lys-Pro-NH₂

[0175] Can be prepared according to Example 1, with the exception that Fmoc-Lys(Boc) and Fmoc-Pro are used prior to step 1. Fmoc-Arg(Pbf) is not used in step 8.

EXAMPLE 37

Synthesis of Compound No. 36: Ac-cyclocys-Glu-His-D-Phe-Arg-Trp-Cys-Ser-Pro-NH₂

[0176] Can be prepared according to Example 1, with the exception that Fmoc-Ser and Fmoc-Pro are used prior to step 1. Fmoc-Arg(Pbf) is not used in step 8.

EXAMPLE 38

Synthesis of Compound No. 37: N-propionyl-cyclocys-Glu-His-D-Phe-Arg-Trp-Cys-NH₂

[0177] Can be prepared according to Example 1, with the exception that step 8 is not carried out. In addition, step 9 is carried out with propionic acid/DCC/HOBt instead of acetic anhydride.

EXAMPLE 39

Synthesis of Compound No. 38: N-butyryl-cyclocys-Glu-His-D-Phe-Arg-Trp-Cys-NH₂

[0178] Can be prepared according to Example 1, with the exception that step 8 is not carried out. In addition, step 9 is carried out with butyric acid/DCC/HOBt instead of acetic anhydride.

EXAMPLE 40

Synthesis of Compound No. 39: N-valeryl-cyclocys-Glu-His-D-Phe-Arg-Trp-Cys-NH₂

[0179] Can be prepared according to Example 1, with the exception that step 8 is not carried out. In addition, step 9 is carried out with valeric acid/DCC/HOBt instead of acetic anhydride.

EXAMPLE 41

Synthesis of Compound No. 40: 3-guanidinopropionyl-cyclocys-Glu-His-D-Phe-Arg-Trp-Cys-NH₂

[0180] The peptide resin Cys(Trt)Glu(OtBu)His(Trt)-D-Phe-Arg(Pbf)Trp(Boc)Cys(Trt)-Rink-PS is assembled by standard Fmoc chemistry as previously described. The resin is then treated with a threefold excess of commercially obtained FmocHNC₃CH₂CH₂COOH activated with DCC/HOBt in DMF for 1.5 hrs. The Fmoc group is removed with 30% piperidine in DMF, and the resin washed with additional DMF and DCM. The resin is then suspended in NMP and treated with 2.0 equivalents of N,N-di[(Boc)-1-guanidinobutyryl]-2 equivalents of DIEA in NMP shaken overnight at room temperature. (Bernatowicz, Wu, and Matsueda, J. Org. Chem. 57(8):2497-2502, 1992).

[0181] The resin is washed extensively with NMP, DCM, and MeOH. A subsequent ninhydrin test for free amine is negative. The resin is cleaved, deprotected, and the resulting peptide cyclized and purified as previously described.

EXAMPLE 42

Synthesis of Compound No. 41: 4-guanidinobutyryl-cyclocys-Glu-His-D-Phe-Arg-Trp-Cys-NH₂

[0182] The peptide is prepared as in Example 40 above with the exception that FmocHNC₃CH₂CH₂COOH is utilized in place of FmocHNC₃CH₂CH₂COOH.

EXAMPLE 43

Synthesis of Compound No. 42: 5-guanidinovaleryl-cyclocys-Glu-His-D-Phe-Arg-Trp-Cys-NH₂

[0183] The peptide is prepared as in Example 40 above with the exception that FmocHNC₃CH₂CH₂CH₂COOH is utilized in place of FmocHNC₃CH₂CH₂COOH.

EXAMPLE 44

Synthesis of Compound No. 43: Ac-Day-cyclocys-Glu-His-D-Phe-Arg-Trp-Cys-NH₂

[0184] Can be prepared according to Example 1, with the exception that the Arg-Cys-Glu-His-D-Phe-Arg-Trp-Cys resin is not treated with acetic anhydride, but instead with 3.0 equivalents of 4,4'-dinitro-α-phenyl-diaminobutyric acid activated with DCC/HOBt. The N-terminal Fmoc group is removed by treatment with 30% piperidine in DMF. The free N-terminus is treated with 5 equivalents of acetic anhydride and 10 equivalents DIEA in dry DMF for 1 hour at room temperature. Resin cleavage, cyclization, and purification are carried out as in Example 1.

EXAMPLE 45

Synthesis of Compound No. 44: Ac-Dab-cyclocys-Glu-His-D-Phe-Arg-Trp-Cys-NH₂

[0185] Can be prepared according to Example 1, with the exception that the Arg-Cys-Glu-His-D-Phe-Arg-Trp-Cys resin is not treated with acetic anhydride, but instead with 3.0 equivalents of 4,4'-dinitro-α-phenyl-diaminobutyric acid activated with DCC/HOBt. The N-terminal Fmoc group is removed by treatment with 30% piperidine in DMF. The free N-terminus is treated with 5 equivalents of acetic anhydride and 10 equivalents DIEA in dry DMF for 1 hour at room temperature. Resin cleavage, cyclization, and purification are carried out as in Example 1.

EXAMPLE 46

Synthesis of Compound No. 45: Arg-cyclocys-Glu-His-D-Phe-Arg-Trp-Cys-OH

[0186] Can be prepared according to Example 1, with the exception that acetylation with acetic anhydride in step 9 is not used. In addition, Wang resin is used instead of Rink resin.
EXAMPLE 47

Synthesis of Compound No. 46: D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0187] Can be prepared according to Example 1, with the exception that Fmoc-Arg(pbf) in step 8 is replaced with Fmoc-D-Arg(pbf). In addition, step 9 of acetylation with acetic acid anhydride is not carried out.

EXAMPLE 48

Synthesis of Compound No. 47: Ac-D-Arg-cyclo [Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0188] Can be prepared according to Example 1, with the exception that Fmoc-D-Phe in step 4 and Fmoc-Arg(pbf) in step 8 are replaced with Fmoc-Phe and Fmoc-D-Arg(pbf), respectively.

EXAMPLE 49

Synthesis of Compound No. 48: Ac-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0189] Can be prepared according to Example 1.

EXAMPLE 50

Synthesis of Compound No. 49: Ac-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH

[0190] Can be prepared according to Example 1, with the exception that Wang resin is used instead of Rink resin.

EXAMPLE 51

Synthesis of Compound No. 50: Ac-Arg-cyclo[Cys-Glu-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH₂

[0191] Can be prepared according to Example 1, with the exception that Fmoc-4-Cl-D-Phe is used in step 4 instead of Fmoc-D-Phe.

EXAMPLE 52

Synthesis of Compound No. 51: Ac-Arg-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH₂

[0192] Can be prepared according to Example 1, with the exception that Fmoc-(1-Me-His) is used in step 5 instead of Fmoc-His(Trt). Due to the unprotected side chain of Fmoc-(1-Me-His), this residue is racemized during the coupling, which affords two peptides:

[0193] Ac-Arg-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH₂, and Ac-Arg-cyclo[Cys-Glu-(1-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH₂

[0194] The two peptide-isomers are easily separated on HPLC. The absolute configurations of the 1-Me-His residue in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXAMPLE 53

Synthesis of Compound No. 52: Ac-D-Arg-cyclo [Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0195] Can be prepared according to Example 1, with the exception that Fmoc-D-Arg(pbf) is used in step 8 instead of Fmoc-Arg(pbf).

EXAMPLE 54

Synthesis of Compound No. 53: Ac-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH

[0196] Can be prepared according to Example 1, with the exception that Fmoc-D-Arg(pbf) is used instead of Fmoc-Arg(pbf) in step 8. In addition, Wang resin is used instead of Rink resin.

EXAMPLE 55

Synthesis of Compound No. 54: Ac-hArg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0197] Can be prepared according to Example 1, with the exception that Fmoc-hArg(Pbf) is used in step 8 instead of Fmoc-Arg(Pbf).

EXAMPLE 56

Synthesis of Compound No. 55: Ac-Cit-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0198] Can be prepared according to Example 1, with the exception that Fmoc-Cit is used in step 8 instead of Fmoc-Arg(Pbf).

EXAMPLE 57

Synthesis of Compound No. 56: Ac-Cit-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH₂

[0199] Can be prepared according to Example 1, with the exception that Fmoc-1-Me-His is used in step 5 instead of Fmoc-His(Trt). Fmoc-Cit is used instead of Fmoc-Arg(Pbf) in step 8. Due to the unprotected side chain of Fmoc-(1-Me-His), this residue is racemized during the coupling, which affords two peptides:

[0200] Ac-Cit-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH₂, and Ac-Cit-cyclo[Cys-Glu-(1-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH₂

[0201] The two peptide-isomers are easily separated on HPLC. The absolute configurations of the 1-Me-His residue in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXAMPLE 58

Synthesis of Compound No. 57: Ac-Leu-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0202] Can be prepared according to Example 1, with the exception that Fmoc-Leu is used instead of Fmoc-Arg(Pbf) in step 8.

EXAMPLE 59

Synthesis of Compound No. 58: Ac-Lys-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0203] Can be prepared according to Example 1, with the exception that Fmoc-Lys(Boc) is used in step 8 instead of Fmoc-Arg(Pbf).
EXAMPLE 60

Synthesis of Compound No. 59: Ac-Lys(ipr)-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0204] Can be prepared according to Example 1 with the exception that Fmoc-Lys(ipr)(Boc) is used instead of Fmoc-Arg(Pbf).

EXAMPLE 61

Synthesis of Compound No. 60: Ac-nLeu-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0205] Can be prepared according to Example 1, with the exception that Fmoc-nLeu is used instead of Fmoc-Arg(Pbf) in step 8.

EXAMPLE 62

Synthesis of Compound No. 61: Ac-nLeu-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser-Pro-NH₂

[0206] Can be prepared according to Example 1, with the exception that Fmoc-Ser and Fmoc-Pro are used prior to step 1. In addition, Fmoc-nLeu is used instead of Fmoc-Arg(Pbf) in step 8.

EXAMPLE 63

Synthesis of Compound No. 62: Ac-Orn-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0207] Can be prepared according to Example 1, with the exception that Fmoc-Orn is used in step 8 instead of Fmoc-Arg(Pbf).

EXAMPLE 64

Synthesis of Compound No. 63: Ac-Val-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0208] Can be prepared according to Example 1, with the exception that Fmoc-Val is used instead of Fmoc-Arg(Pbf) in step 8.

EXAMPLE 65

Synthesis of Compound No. 64: N-(2-naphthalenesulfonyl)-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0209] Can be prepared according to Example 1, with the exception that Fmoc-Arg(pbf) in step 8 and acetic anhydride in step 9 are replaced with Fmoc-D-Arg(pbf) and 2-naphthalenesulfonylchloride, respectively.

EXAMPLE 66

Synthesis of Compound No. 65: N-(4-(2-naphthalenesulfonylazo)-4-oxo-butyryl)-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0210] Can be prepared according to Example 1, with the exception that Fmoc-Arg(pbf) in step 8 and acetic anhydride in step 9 are replaced with Fmoc-D-Arg(pbf) and succinic anhydride, respectively. Attaching the naphthalene 2-sulfonyamide is carried out as follows: after step 9, the resin is swollen in DCM and washed several times with dry DMF.

Then, 5 equivalents of naphthalene 2'-sulfonamide, 10 equivalents of PyBOP, and 10 equivalents of DIEA in dry DMF are added to the resin with a catalytic amount of DMAP (4-(N,N-diethylamino)pyridine). The coupling reaction is allowed to proceed at room temperature for 3 h, and the resin is washed and dried.

EXAMPLE 67

Synthesis of Compound No. 66: 3-(4-hydroxyphenyl)propionyl-Arc-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0211] Can be prepared according to Example 1, with the exception that the Arg-Cys-Glu-His-D-Phe-Arg-Trp-Cys resin is not treated with acetic anhydride, but instead with an excess of 3-(4-hydroxyphenyl)propionic acid activated with DCC/HOBt. The cyclization and purification are carried out as in Example 1.

EXAMPLE 68

Synthesis of Compound No. 67: 3-(4-methylbenzoyl)propionyl-Arc-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0212] Can be prepared according to Example 1, with the exception that the Arg-Cys-Glu-His-D-Phe-Arg-Trp-Cys resin is not treated with acetic anhydride, but instead with an excess of 3-(4-methylbenzoyl)propionic acid activated with DCC/HOBt. The cyclization and purification are carried out as in Example 1.

EXAMPLE 69

Synthesis of Compound No. 68: Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0213] Can be prepared according to Example 1, with the exception that acetylation with acetic anhydride in step 9 is not used. Fmoc-Tyr(tBu) is added after step 8.

EXAMPLE 70

Synthesis of Compound No. 69: Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH

[0214] Can be prepared according to Example 1, with the exception that acetylation with acetic anhydride in step 9 is not used. Fmoc-Tyr(tBu) is added after step 8. In addition, Wang resin is used instead of Rink resin.

EXAMPLE 71

Synthesis of Compound No. 70: Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₃—(CH₃)₁₅—NH₂

[0215] Can be prepared according to Example 1, with the exception that 1,6-diaminoheptane trityl resin (Nash, Bycroft, and Chan, Tet. Lett. 37(15):2625-28, 1996) is used instead of Rink resin. In addition, step 9 is not carried out.

EXAMPLE 72

Synthesis of Compound No. 71: Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Glu-NH₂

[0216] Can be prepared according to Example 1, with the exception that Fmoc-Glu is used prior to step 1. Fmoc-
Tyr(Bu) is added after step 8. Acetylation with acetic anhydride in step 9 is omitted.

EXAMPLE 73
Synthesis of Compound No. 72: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0217] Can be prepared according to Example 1, with the exception that Fmoc-Tyr(Bu) is added between steps 8 and 9.

EXAMPLE 74
Synthesis of Compound No. 73: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH

[0218] Can be prepared according to Example 1, with the exception that Fmoc-Tyr(Bu) is added between steps 8 and 9. Wang resin is used instead of Rink resin.

EXAMPLE 75
Synthesis of Compound No. 74: N-succinyl-Tyr-
Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0219] Can be prepared according to Example 1, with the exception that step 9 is carried out with succinyl anhydride instead of acetic anhydride. Fmoc-Tyr(Bu) is added between steps 8 and 9.

EXAMPLE 76
Synthesis of Compound No. 75: N-glutarlyl-Tyr-
Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0220] Can be prepared according to Example 1, with the exception that step 9 is carried out with glutaryl anhydride instead of acetic anhydride. Fmoc-Tyr(Bu) is added between steps 8 and 9.

EXAMPLE 77
Synthesis of Compound No. 76: N-glutarlyl-Tyr-
Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH

[0221] Can be prepared according to Example 1, with the exception that step 9 is carried out with glutaryl anhydride instead of acetic anhydride. Fmoc-Tyr(Bu) is added between steps 8 and 9. Wang resin is used instead of Rink resin.

EXAMPLE 78
Synthesis of Compound No. 77: N-glucono-Tyr-
Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0222] Can be prepared according to Example 1, with the exception that step 9 is not carried out. Fmoc-Tyr(Bu) is added between steps 8 and 9. The peptide is dissolved in DMF and reacted with glutonolactone/DMAP overnight. The final product is then purified.

EXAMPLE 79
Synthesis of Compound No. 78: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-alcohol

[0223] Commercially available Fmoc-Cys(Trt) alcohol is attached to commercially available trichloroacetimidate derivatized Wang resin according to published procedure (Yan and Mayer, J. Org. Chem. 68(3):1161-62, 2003). The peptide chain is then extended in the conventional manner to obtain the resin-bound Tyr-Arg-Cys-Glu-His-D-Phe-Arg-Trp-Cys alcohol sequence. Acetylation of the α-amino group is carried out as above with 5 equivalents of acetic anhydride and 10 equivalents DIEA in dry DMF for 1 hour at room temperature. Resin cleavage, cyclization, and purification are carried out as in the above examples.

EXAMPLE 80
Synthesis of Compound No. 79: Ac-Tyr-D-Arg-
cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0224] Can be prepared according to Example 1, with the exception that Fmoc-D-Arg(Ph) is used instead of Fmoc-Arg(Ph) in step 8. Fmoc-Tyr(Bu) is added between steps 8 and 9.

EXAMPLE 81
Synthesis of Compound No. 80: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0225] Can be prepared according to Example 1, with the exception that Fmoc-D-Cys is used in step 7 instead of Fmoc-Cys(Trt). Fmoc-Tyr(Bu) is added between steps 8 and 9.

EXAMPLE 82
Synthesis of Compound No. 81: Ac-Tyr-Arg-cyclo
[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH₂ and
Synthesis of Compound No. 82: Ac-Tyr-Arg-cyclo
[Cys-Glu-(1-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH₂

[0226] Can be prepared according to Example 1, with the exception that Fmoc-(1-Me-His) is used in step 5 instead of Fmoc-His(Trt). In addition, Fmoc-Tyr(Bu) is added between steps 8 and 9. Due to the unprotected side chain of Fmoc-(1-Me-His), this residue is racemized during the coupling, which affords two peptides:

[0227] Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-D-Phe-
Arg-Trp-Cys]-NH₂ and Ac-Tyr-Arg-cyclo[Cys-Glu-(1-
Me-D-His)-D-Phe-Arg-Trp-Cys]-NH₂

[0228] The two peptide-isomers are easily separated on HPLC. The absolute configurations of the 1-Me-His residue in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXAMPLE 83
Synthesis of Compound No. 84: Ac-Tyr-Arg-cyclo
[Cys-Glu-(1-Me-His)-(4-F-D-Phe)-Arg-Trp-Cys]-
NH₂ and Synthesis of Compound No. 85: Ac-Tyr-
Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-F-D-Phe)-Arg-
Trp-Cys]-NH₂

[0229] Can be prepared according to Example 1, with the exception that Fmoc-1-Me-His is used in step 5 instead of Fmoc-His(Trt). Fmoc-4-F-D-Phe is used instead of Fmoc-D-Phe in step 4. Fmoc-Tyr(Bu) is added between steps 8 and 9. Due to the unprotected side chain of Fmoc-(1-Me-
His), this residue is racemized during the coupling, which affords two peptides:
[0230] Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-F-D-Phe)-Arg-Trp-Cys]-NH₂ and Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-F-D-Phe)-Arg-Trp-Cys]-NH₂.

[0231] The two peptide-isomers are easily separated on HPLC. The absolute configurations of the 1-Me-His residue in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXEMPLARY

Synthesis of Compound No. 86: Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH₂

[0232] Can be prepared according to Example 1, with the exception that Fmoc-4-Cl-D-Phe is used in step 4 instead of Fmoc-D-Phe. In addition, Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXEMPLARY 85

Synthesis of Compound No. 87: Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH₂ and Synthesis of Compound No. 88: Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH₂

[0233] Can be prepared according to Example 1, with the exception that Fmoc-4-Cl-D-Phe is used in step 4 instead of Fmoc-D-Phe and Fmoc-(1-Me-His) is used in step 5 instead of Fmoc-His(Trt), respectively. In addition, Fmoc-Tyr(tBu) is added between steps 8 and 9. Due to the unprotected side chain of Fmoc-(1-Me-His), this residue is racemized during the coupling, which affords two peptides:

[0234] Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH₂ and Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH₂.

[0235] The two peptide-isomers are easily separated on HPLC. The absolute configurations of the 1-Me-His residue in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXEMPLARY 86

Synthesis of Compound No. 89: Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-Br-D-Phe)-Arg-Trp-Cys]-NH₂

[0236] Can be prepared according to Example 1, with the exception that Fmoc-4-Br-D-Phe is used instead of Fmoc-D-Phe in step 4. Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXEMPLARY 87

Synthesis of Compound No. 90: Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-Br-D-Phe)-Arg-Trp-Cys]-NH₂ and Synthesis of Compound No. 91: Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-Br-D-Phe)-Arg-Trp-Cys]-NH₂

[0237] Can be prepared according to Example 1, with the exception that Fmoc-4-Br-D-Phe is used in step 4 instead of Fmoc-D-Phe and Fmoc-(1-Me-His) is used in step 5 instead of Fmoc-His(Trt), respectively. In addition, Fmoc-Tyr(tBu) is added between steps 8 and 9. Due to the unprotected side chain of Fmoc-(1-Me-His), this residue is racemized during the coupling, which affords two peptides:


[0239] The two peptide-isomers are easily separated on HPLC. The absolute configurations of the 1-Me-His residue in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXEMPLARY 88

Synthesis of Compound No. 92: Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-Br-D-Phe)-Arg-Trp-Cys]-NH₂

[0240] Can be prepared according to Example 1, with the exception that Fmoc-4-Br-D-Phe is used in step 4 instead of Fmoc-D-Phe. Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXEMPLARY 89

Synthesis of Compound No. 93: Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-O-Me-D-Phe)-Arg-Trp-Cys]-NH₂

[0241] Can be prepared according to Example 1, with the exception that Fmoc-4-O-Me-D-Phe is used in step 4 instead of Fmoc-D-Phe. Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXEMPLARY 90


[0242] Can be prepared according to Example 1, with the exception that Fmoc-1-Me-His is used in step 5 instead of Fmoc-His(Trt). Fmoc-4-O-Me-D-Phe is used instead of Fmoc-D-Phe in step 4. Fmoc-Tyr(tBu) is added between steps 8 and 9. Due to the unprotected side chain of Fmoc-(1-Me-His), this residue is racemized during the coupling, which affords two peptides:


[0244] The two peptide-isomers are easily separated on HPLC. The absolute configurations of the 1-Me-His residue in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXEMPLARY 91

Synthesis of Compound No. 96: Ac-Tyr-Arg-cyclo[Cys-Glu(3-Me-His)-(D-Phe)-Arg-Trp-Cys]-NH₂

[0245] Can be prepared according to Example 1, with the exception that Fmoc-3-Me-His is used in step 5 instead of Fmoc-His(Trt). Fmoc-Tyr(tBu) is added between steps 8 and 9.
EXAMPLE 92
Synthesis of Compound No. 99: Ac-Tyr-Arg-cyclo
[Cys-Glu-(1-Bz1-His)-D-Phe-Arg-Trp-Cys]-NH2
Synthesis of Compound No. 100: Ac-Tyr-Arg-cyclo
[Cys-Glu-(1-Bz1-His)-DPhe-Arg-Trp-Cys]-NH2
[0246] Can be prepared according to Example 1, with the exception that Fmoc-1-Bz1-His is used in step 5 instead of Fmoc-His(Trt). Fmoc-Tyr(tBu) is added between steps 8 and 9. Due to the unprotected side chain of Fmoc-(1-Bz1-His), this residue is racemized during the coupling, which affords two peptides:

<table>
<thead>
<tr>
<th>[0247] Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Bz1-His)-D-Phe-Arg-Trp-Cys]-NH2</th>
<th>Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Bz1-His)-D-Phe-Arg-Trp-Cys]-NH2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The two peptide isomers are easily separated on HPLC. The absolute configurations of the 1-Bz1-His residue in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.</td>
</tr>
</tbody>
</table>

EXAMPLE 93
Synthesis of Compound No. 101: Ac-Tyr-Arg-cyclo
[Cys-Glu-(1-Bom-His)-D-Phe-Arg-Trp-Cys]-NH2
[0249] Can be prepared according to Example 1, with the exception that Fmoc-1-Bom-His is used in step 5 instead of Fmoc-His(Trt). Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 94
Synthesis of Compound No. 110: Ac-Tyr-Arg-cyclo
[Cys-Glu-(1-((2-furyl)-ala)-D-Phe-Arg-Trp-Cys)-NH2
[0250] Can be prepared according to Example 1, with the exception that Fmoc-β-(2-furyl)-ala is used in step 5 instead of Fmoc-His(Trt). In addition, Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 95
Synthesis of Compound No. 111: Ac-Tyr-Arg-cyclo
[Cys-Glu-(β-(thien-2-yl)-ala)-D-Phe-Arg-Trp-Cys]-NH2
[0251] Can be prepared according to Example 1, with the exception that Fmoc-β-(thien-2-yl)-ala is used in step 5 instead of Fmoc-His(Trt). In addition, Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 96
Synthesis of Compound No. 112: Ac-Tyr-Arg-cyclo
[Cys-Glu-(β-(1,3-thiazol-4-yl)-ala)-D-Phe-Arg-Trp-Cys]-NH2
[0252] Can be prepared according to Example 1, with the exception that Fmoc-β-(1,3-thiazol-4-yl)-ala is used in step 5 instead of Fmoc-His(Trt). In addition, Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 97
Synthesis of Compound No. 113: Ac-Tyr-Arg-cyclo
[Cys-Glu-(β-(pyridin-4-yl)-ala)-D-Phe-Arg-Trp-Cys]-NH2
[0253] Can be prepared according to Example 1, with the exception that Fmoc-β-(pyridin-4-yl)-ala is used in step 5 instead of Fmoc-His(Trt). In addition, Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 98
Synthesis of Compound No. 114: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-glycine
[0254] Can be prepared according to Example 1, with the exception that glycineol 2-chlorotriyl resin (Barbos, Chatzi, Gatos, and Stavropoulos, Int. J. Pept. Protein Res. 37(6):513-20, 1991) is used instead of Rink resin.

EXAMPLE 99
Synthesis of Compound No. 115: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-2-(2-aminoethoxy)ethanol
[0255] Can be prepared according to Example 1, with the exception that 2-(2-aminoethoxy) ethanol 2-chlorotriyl resin (Barbos, Chatzi, Gatos, and Stavropoulos, Int. J. Pept. Protein Res. 37(6):513-20, 1991) is used instead of Rink resin.

EXAMPLE 100
Synthesis of Compound No. 116: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser alcohol
[0256] Can be prepared according to Example 1, with the exception that Wang resin is used instead of Rink resin. Wang resin was preloaded with Fmoc-serino(tBu) according to a published method (Yan and Mayer, J. Org. Chem. 68:1161-62, 2003) prior to step 1. Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 101
Synthesis of Compound No. 117: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH2—(CH2)n—NH2
[0257] Can be prepared according to Example 1, with the exception that 1,6-diaminohexane trityl resin (Nash, Bycroft, and Chan, Tet. Lett. 37(15):2625-28, 1996) is used instead of Rink resin.

EXAMPLE 102
Synthesis of Compound No. 118: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Glu-NH2
[0258] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OhBu) is used prior to step 1. Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 103
Synthesis of Compound No. 119: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser-Pro-NH2
[0259] Can be prepared according to Example 1, with the exception that Fmoc-Ser and Fmoc-Pro are used prior to step 1. In addition, Fmoc-Tyr is used between steps 8 and 9.

EXAMPLE 104
Synthesis of Compound No. 120: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser-Pro alcohol
[0260] Can be prepared according to Example 1, with the exception that Wang resin is used instead of Rink resin.
Wang resin was preloaded with Fmoc-prolinol according to a published method (Yan and Mayer, J. Org. Chem. 68:1161-62, 2003), and then Fmoc-Sert(tBu) was added prior to step 1. In addition, Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 105

Synthesis of Compound No. 121: Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Lys-Pro-NH$_2$

[0261] Can be prepared according to Example 1, with the exception that Fmoc-Lys(Boc) and Fmoc-Pro are used prior to step 1. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 106

Synthesis of Compound No. 122: Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Lys-Pro alcohol

[0262] Can be prepared according to Example 1, with the exception that Wang resin is used instead of Rink resin. Wang resin was preloaded with Fmoc-prolinol according to a published method (Yan and Mayer, J. Org. Chem. 68:1161-62, 2003), and then Fmoc-Lys(Boc) was added prior to step 1. In addition, Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 107

Synthesis of Compound No. 123: Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Arg-Phe-NH$_2$

[0263] Can be prepared according to Example 1, with the exception that Fmoc-Arg(Pbf) and Fmoc-Phe are used prior to step 1. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 108

Synthesis of Compound No. 124: Ac-Tyr-Cit-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH$_2$

[0264] Can be prepared according to Example 1, with the exception that Fmoc-Cit is used instead of Fmoc-Arg(Pbf) in step 8, and Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 109

Synthesis of Compound No. 125: Ac-Tyr-Cit-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH$_2$ and Synthesis of Ac-Tyr-Cit-cyclo[Cys-Glu-(1-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH$_2$

[0265] Can be prepared according to Example 1, with the exception that Fmoc-1-Me-His is used in step 5 instead of Fmoc-His(Trt). Fmoc-Cit is used instead of Fmoc-Arg(Pbf) in step 8. Fmoc-Tyr(tBu) is added between steps 8 and 9. Due to the unprotected side chain of Fmoc-(1-Me-His), this residue is racemized during the coupling, which affords two peptides:

[0266] Ac-Tyr-Cit-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH$_2$ and Ac-Tyr-Cit-cyclo[Cys-Glu-(1-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH$_2$.

[0267] The two peptide-isomers are easily separated on HPLC. The absolute configurations of the 1-Me-His residue in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXAMPLE 110

Synthesis of Compound No. 126: Ac-Tyr-hArg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH$_2$

[0268] Can be prepared according to Example 1, with the exception that Fmoc-hArg(Pbf) is used in step 8 instead of Fmoc-Arg(Pbf). Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 111

Synthesis of Compound No. 127: Ac-Tyr-(1$h$Arg)-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH$_2$

[0269] Can be prepared according to Example 1, with the exception that Fmoc-1$h$Arg(Pbf) is used instead of Fmoc-Arg(Pbf) in step 8. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 112

Synthesis of Compound No. 128: Ac-Tyr-Lys-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH$_2$

[0270] Can be prepared according to Example 1, with the exception that Fmoc-Lys(Boc) is used in step 8 instead of Fmoc-Arg(Pbf). Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 113

Synthesis of Compound No. 129: Ac-Tyr-Ser-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH$_2$

[0271] Can be prepared according to Example 1, with the exception that Fmoc-Ser is used instead of Fmoc-Arg(Pbf) in step 8. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 114

Synthesis of Compound No. 130: Ac-Tyr-Val-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH$_2$

[0272] Can be prepared according to Example 1, with the exception that Fmoc-Val is used instead of Fmoc-Arg(Pbf) in step 8. Fmoc-Tyr(tBu) is used between steps 8 and 9.

EXAMPLE 115

Synthesis of Compound No. 131: N-succinyl-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH

[0273] Can be prepared according to Example 1, with the exception that step 9 is carried out with succinic anhydride instead of acetic anhydride. Fmoc-Tyr(tBu) is added between steps 8 and 9. Wang resin is used instead of Rink resin.

EXAMPLE 116

Synthesis of Compound No. 132: cyclo[Cys-His-D-Phe-Arg-Trp-Cys]-NH$_2$

[0274] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) and Fmoc-Arg(Pbf) in steps 6 and 8, respectively, are not used. In addition, acetylation with acetic anhydride in step 9 is not used. Finally, homocysteine is used instead of cysteine in step 7.
EXAMPLE 117

Synthesis of Compound No. 133: cyclo[\text{cys}-\text{his}-\text{d-phenylalanine}-\text{trypotophan}-\text{cysteine}]\text{-oh}

[0275] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6, Fmoc-Arg(pbf) in step 8, and acetylation with acetic anhydride in step 9 are not used. Homocysteine is used instead of cysteine in step 7. Wang resin is used instead of Rink resin.

EXAMPLE 118

Synthesis of Compound No. 134: cyclo[\text{cys}-\text{his}-(4-\text{f-d-phenylalanine})-\text{trypotophan}-\text{cysteine}]\text{-nh}_2

[0276] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6, Fmoc-Arg(pbf) in step 8, and acetylation with acetic anhydride in step 9 are not used. In addition, Fmoc-hCys(Trt) is used instead of Fmoc-Cys(Trt) in step 7, and Fmoc-(4-f-d-phenylalanine) is used instead of Fmoc-D-Phe in step 4.

EXAMPLE 119

Synthesis of Compound No. 135: cyclo[\text{cys}-\text{his}-(4-\text{ci-d-phenylalanine})-\text{trypotophan}-\text{cysteine}]\text{-nh}_2

[0277] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6, Fmoc-Arg(pbf) in step 8, and acetylation with acetic anhydride in step 9 are not used. In addition, Fmoc-hCys(Trt) is used in step 7, and Fmoc-4-Cl-D-Phe is used instead of Fmoc-D-Phe in step 4.

EXAMPLE 120

Synthesis of Compound No. 136: Ac-\text{cyclo[\text{cys-his-d-phenylalanine}-\text{trypotophan}-\text{cysteine}]\text{-nh}_2}

[0278] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. In addition, Fmoc-D-Phe in step 4 and Fmoc-Cys(Trt) in step 7 are replaced with Fmoc-Phe and Fmoc-hCys(Trt), respectively.

EXAMPLE 121

Synthesis of Compound No. 137: Ac-\text{cyclo[\text{cys-his-d-phenylalanine}-\text{trypotophan}-\text{cysteine}]\text{-nh}_2}

[0279] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) and Fmoc-Arg(Phb) in steps 6 and 8, respectively, are not used. In addition, homocysteine is used instead of cysteine in step 7.

EXAMPLE 122

Synthesis of Compound No. 138: Ac-cyclo[\text{cys-his-d-phenylalanine}-\text{trypotophan}-\text{cysteine}]\text{-oh}

[0280] Can be prepared according to Example 1, with the exception that homocysteine is used instead of cysteine in step 7, and Fmoc-Arg(Phb) is omitted from step 8. Wang resin is used instead of Rink resin.

EXAMPLE 123

Synthesis of Compound No. 139: Ac-cyclo[\text{cys-his}-(4-f-d-phenylalanine)-\text{trypotophan}-\text{cysteine}]\text{-nh}_2

[0281] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6 and Fmoc-Arg-(pbf) in step 8 are not used. In addition, Fmoc-hCys(Trt) and Fmoc-(4-f-d-phenylalanine) are used instead of Fmoc-Cys(Trt) in step 7 and Fmoc-D-Phe in step 4, respectively.

EXAMPLE 124

Synthesis of Compound No. 140: Ac-cyclo[\text{cys-his}-(4-ci-d-phenylalanine)-\text{trypotophan}-\text{cysteine}]\text{-nh}_2

[0282] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) and Fmoc-Arg(pbf) in steps 6 and 8 are not used. In addition, Fmoc-hCys(Trt) and Fmoc-4-Cl-D-Phe are used instead of Fmoc-Cys(Trt) and Fmoc-D-Phe, respectively, in steps 4 and 7.

EXAMPLE 125

Synthesis of Compound No. 141: N-cyclopropanecarbonyl-cyclo[\text{cys-his-d-phenylalanine}-\text{trypotophan}-\text{cysteine}]\text{-nh}_2

[0283] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. Fmoc-Cys(Trt) in step 7 is replaced with Fmoc-hCys(Trt). In addition, in step 9, acetic anhydride is replaced with cyclopropane carboxylic acid, which is pre-activated with DIC (1,3-diisopropylcarbodiimide)/HOBT (1-hydroxybenzotriazole).

EXAMPLE 126

Synthesis of Compound No. 142: N-cyclobutanecarbonyl-cyclo[\text{cys-his-d-phenylalanine}-\text{trypotophan}-\text{cysteine}]\text{-nh}_2

[0284] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. Fmoc-hCys(Trt) is used in step 7 instead of Fmoc-Cys(Trt). In addition, in step 9, acetic anhydride is replaced with cyclobutane carboxylic acid, which is pre-activated with DIC (1,3-diisopropylcarbodiimide)/HOBT (1-hydroxybenzotriazole).

EXAMPLE 127

Synthesis of Compound No. 143: N-cyclopentanecarbonyl-cyclo[\text{cys-his-d-phenylalanine}-\text{trypotophan}-\text{cysteine}]\text{-nh}_2

[0285] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. Fmoc-Cys(Trt) in step 7 is replaced with Fmoc-hCys(Trt). In addition, in step 9, acetic anhydride is replaced with cyclopentane carboxylic acid, which is pre-activated with DIC (1,3-diisopropylcarbodiimide)/HOBT (1-hydroxybenzotriazole).

EXAMPLE 128

Synthesis of Compound No. 144: N-cyclohexanecarbonyl-cyclo[\text{cys-his-d-phenylalanine}-\text{trypotophan}-\text{cysteine}]\text{-nh}_2

[0286] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. Fmoc-hCys(Trt) is used in step 7 instead of Fmoc-Cys(Trt). In addition, in step 9, acetic anhydride is replaced with cyclohexane carboxylic acid,
which is pre-activated with DIC (1,3-diisopropyl-carbodi-imide)/HOBt (1-hydroxybenzotriazole).

**EXAMPLE 129**

Synthesis of Compound No. 145: N-hexanoyl-cyclo [hCys-His-D-Phe-Arg-Trp-Cys]-NH\_2

[0287] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and Fmoc-Arg-(pbf) in step 8 are not used. Fmoc-hCys(Trt) is used in step 7 instead of Fmoc-Cys(Trt). In addition, in step 9 acetic anhydride is replaced with n-hexanoic acid, which is pre-activated with DIC (1,3-diisopropylcarbodi-imide)/HOBt (1-hydroxybenzotriazole).

**EXAMPLE 130**

Synthesis of Compound No. 146: N-benzyoyl-cyclo [hCys-His-D-Phe-Arg-Trp-Cys]-NH\_2

[0288] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and Fmoc-Arg-(pbf) in step 8 are not used. Fmoc-hCys(Trt) is used in step 7 instead of Fmoc-Cys(Trt). In addition, in step 9, acetic anhydride is replaced with benzoic acid, which is pre-activated with DIC (1,3-diisopropylcarbodi-imide)/HOBt (1-hydroxybenzotriazole).

**EXAMPLE 131**

Synthesis of Compound No. 147: 4-phenylbutyril-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH\_2

[0289] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and Fmoc-Arg-(pbf) in step 8 are not used. Fmoc-hCys(Trt) is used in step 7 instead of Fmoc-Cys(Trt). In addition, in step 9, acetic anhydride is replaced with 4-phenylbutyric acid, which is pre-activated with DIC (1,3-diisopropylcarbodi-imide)/HOBt (1-hydroxybenzotriazole).

**EXAMPLE 132**

Synthesis of Compound No. 148: 3-guanidinopropionyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH\_2

[0290] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 is not used. Fmoc-Cys(Trt) in step 7 and Fmoc-Arg(pbf) in step 8 are replaced with Fmoc-hCys(Trt) and Fmoc-β-Ala(Fmoc-3-amino propionic acid), respectively. In addition, step 9, acetylation is replaced with the following treatment (guanidylation): After Fmoc deprotection, the resin is incubated with 10 equivalents of N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and 10 equivalents of DIEA in NMP (N-methylpyrrorolidone) overnight at room temperature.

**EXAMPLE 133**

Synthesis of Compound No. 149: 5-guanidinov-allyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH\_2

[0291] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 is not used. Fmoc-Cys(Trt) in step 7 and Fmoc-Arg(pbf) in step 8 are replaced with Fmoc-hCys(Trt) and Fmoc-5-amino-valeric acid, respectively. In addition, step 9, acetylation is replaced with the following treatment (guanidylation): After Fmoc deprotection, the resin is incubated with 10 equivalents of N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and 10 equivalents of DIEA in NMP (N-methylpyrrorolidone) overnight at room temperature.

**EXAMPLE 134**

Synthesis of Compound No. 150: N-phenylsulfon-yl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH\_2

[0292] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and Fmoc-Arg-(pbf) in step 8 are not used. In addition, Fmoc-hCys(Trt) in step 7 used instead of Fmoc-Cys(Trt). Acetic anhydride in step 9 is replaced with phenylsulfonylchloride.

**EXAMPLE 135**

Synthesis of Compound No. 151: N-(2-naphthalenesulfonyl)-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH\_2

[0293] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and Fmoc-Arg-(pbf) in step 8 are not used. In addition, Fmoc-hCys(Trt) in step 7 used instead of Fmoc-Cys(Trt). Acetic anhydride in step 9 is replaced with 2-naphthalenesulfonylchloride.

**EXAMPLE 136**

Synthesis of Compound No. 152: N-(4-phenylsulfonylamido-4-oxo-butyryl)-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH\_2

[0294] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and Fmoc-Arg-(pbf) in step 8 are not used. Fmoc-hCys(Trt) is used in step 7 instead of Fmoc-Cys(Trt). In step 9, acetic anhydride is replaced with succinic acid anhydride. In addition, one more step is added after step 9. Attaching the phenylsulfonynamide is as follows: after the step 9, the resin is swollen in DCM and washed several times with dry DME. Then, 5 equivalents of phenylsulfonylamide, 10 equivalents of PyBOP, and 10 equivalents of DIEA in dry DME are added to the resin with a catalytic amount of DMAP (4-(N,N'-dimethylami-no)pyridine). The coupling reaction is allowed to proceed at room temperature for 3 h, and the resin is then washed and dried.

**EXAMPLE 137**

Synthesis of Compound No. 153: Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH\_2

[0295] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) and acetylation with acetic anhydride in steps 6 and 9, respectively, are not used. In addition, homocysteine is used instead of cysteine in step 7.

**EXAMPLE 138**

Synthesis of Compound No. 154: D-Arg-cyclo [hCys-His-D-Phe-Arg-Trp-Cys]-NH\_2

[0296] Can be prepared according to Example 1, with the exception that Fmoc-Arg(pbf) in step 8 is replaced with Fmoc-D-Arg(pbf) and Fmoc-Glu(OrBu), and acetylation
with acetic anhydride in steps 6 and 9, respectively, are not used. Finally, homocysteine is used instead of cysteine in step 7.

EXAMPLE 139

Synthesis of Compound No. 155:
Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH

[0297] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) acetylation with acetic anhydride in steps 6 and 9, respectively, are not used. In addition, Wang resin is used instead of Rink resin. Finally, homocysteine is used instead of cysteine in step 7.

EXAMPLE 140


[0298] Can be prepared according to Example 1, with the exception that Fmoc-(1-Me-His) is used in step 5 instead of Fmoc-His(Trr). Fmoc-hCys(Trr) is used instead of Fmoc-Cys(Trr) in step 6. In addition, acetylation with acetic anhydride in step 9 is not used. Due to the unprotected side chain of Fmoc-(1-Me-His), this residue is racemized during the coupling, which affords two peptides:


[0300] The two peptide-isomers are easily separated on HPLC. The absolute configurations of the 1-Me-His residue in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXAMPLE 141

Synthesis of Compound No. 158: Ac-Arg-cyclo
[hCys-His-D-Phe-Arg-Trp-Cys]-NH₂

[0301] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 is not used. In addition, homocysteine is used instead of cysteine in step 7.

EXAMPLE 142

Synthesis of Compound No. 159: Ac-Arg-cyclo
[hCys-His-D-Phe-Arg-Trp-Cys]-OH

[0302] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 is not used. In addition, homocysteine is used instead of cysteine in step 7. Finally, Wang resin is used instead of Rink resin.

EXAMPLE 143

Synthesis of Compound No. 160: Ac-nLeu-cyclo
[hCys-His-D-Phe-Arg-Trp-Cys]-NH₂

[0303] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 is not used. Fmoc-Cys(Trr) in step 7 and Fmoc-Arg(pbf) in step 8 are replaced with Fmoc-hCys(Trr) and Fmoc-nLeu, respectively.

EXAMPLE 144

Synthesis of Compound No. 161: N-phenylsulfonfyl-Gly-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH₂

[0304] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 is not used. In addition, Fmoc-hCys(Trr) and Fmoc-Gly are used in steps 7 and 8 instead of Fmoc-Cys(Trr) and Fmoc-Arg(pbf), respectively. Acetic anhydride in step 9 is replaced with phenyl-sulfonyl chloride.

EXAMPLE 145

Synthesis of Compound No. 162: Tyr-Arg-cyclo
[hCys-His-D-Phe-Arg-Trp-Cys]-OH

[0305] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) and acetylation with acetic anhydride in steps 6 and 9, respectively, are not used. In addition, Fmoc-Tyr(tBu) is added between steps 8 and 9. Finally, homocysteine is used instead of cysteine in step 7.

EXAMPLE 146

Synthesis of Compound No. 163: Tyr-Arg-cyclo
[hCys-His-D-Phe-Arg-Trp-Cys]-OH

[0306] Can be prepared according to Example 1, with the exception that acetylation with acetic anhydride in step 9 is not used, and homocysteine is used instead of cysteine in step 7. In addition, Fmoc-Tyr(tBu) is added after step 8. Finally, Wang resin is used instead of Rink resin.

EXAMPLE 147

Synthesis of Compound No. 164: Ac-Tyr-Arg-cyclo
[hCys-His-D-Phe-Arg-Trp-Cys]-OH

[0307] Can be prepared according to Example 1, with the exception that homocysteine is used instead of cysteine in step 7. Fmoc-Glu(OrBu) is not used in step 6. Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 148

Synthesis of Compound No. 165: Ac-Tyr-Arg-cyclo
[hCys-His-D-Phe-Arg-Trp-Cys]-OH

[0308] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) is not used. In addition, homocysteine is used instead of cysteine in step 7. Fmoc-Tyr(tBu) is added after step 8. Finally, Wang resin is used instead of Rink resin.

EXAMPLE 149

Synthesis of Compound No. 166: Ac-Tyr-Arg-cyclo
[hCys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂

[0309] Can be prepared according to Example 1, with the exception that Fmoc-Tyr(tBu) is used between steps 8 and 9. Homocysteine is used instead of cysteine in step 7.

EXAMPLE 150

Synthesis of Compound No. 167: Ac-cyclo[hCys-His-(β-cyclohexyl-D-Ala)-Arg-Trp-Cys]-NH₂

[0310] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and Fmoc-Arg-
(pbf) in step 8 are not used. In addition, Fmoc-hCys(Trt) and Fmoc-(β-cyclohexyl-D-Ala) are used instead of Fmoc-Cys(Trt) in step 7 and Fmoc-D-Phe in step 4, respectively.

**EXAMPLE 151**

Synthesis of Compound No. 168: Ac-cyclo[His-D-Phe-Arg-Trp-penicillamine]-NH₂

**[0311] Can be prepared according to Example 1, with the exception that Fmoc-Glu(ObtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. In addition, Fmoc-penicillamine(Trt) and Fmoc-hCys(Trt) are used instead of Fmoc-Cys(Trt) in steps 1 and 7, respectively.**

**EXAMPLE 152**

Synthesis of Compound No. 169: Ac-cyclo[His-(4-Cl-D-Phe)-Arg-Trp-penicillamine]-NH₂

**[0312] Can be prepared according to Example 1, with the exception that Fmoc-Glu(ObtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. Fmoc-Cys(Trt) in steps 1 and 7, and Fmoc-D-Phe in step 4 are replaced with Fmoc-penicillamine(Trt), Fmoc-hCys(Trt), and Fmoc-4-Cl-D-Phe, respectively.**

**EXAMPLE 153**

Synthesis of Compound No. 170: N-hexanoyl-cyclo [His-D-Phe-Arg-Trp-penicillamine]-NH₂

**[0313] Can be prepared according to Example 1, with the exception that Fmoc-Glu(ObtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. Fmoc-hCys(Trt) and Fmoc-penicillamine(Trt) are used in steps 7 and 1, respectively, instead of Fmoc-Cys(Trt). In addition, in step 9, acetic anhydride is replaced with n-hexanoic acid, which is pre-activated with DIC (1,3-diisopropylcarbodiimide)/HOBT (1-hydroxybenzotriazole).**

**EXAMPLE 154**

Synthesis of Compound No. 171: N-cyclopentanecarbonyl-cyclo[His-D-Phe-Arg-Trp-penicillamine]-NH₂

**[0314] Can be prepared according to Example 1, with the exception that Fmoc-Glu(ObtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. Fmoc-Cys(Trt) in steps 1 and 7 are replaced with Fmoc-penicillamine(Trt) and Fmoc-hCys(Trt), respectively. In addition, in step 9, acetic anhydride is replaced with cyclopentane carboxylic acid, which is pre-activated with DIC (1,3-diisopropylcarbodiimide)/HOBT (1-hydroxybenzotriazole).**

**EXAMPLE 155**

Synthesis of Compound No. 172: N-cyclohexanecarbonyl-cyclo[His-D-Phe-Arg-Trp-penicillamine]-NH₂

**[0315] Can be prepared according to Example 1, with the exception that Fmoc-Glu(ObtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. Fmoc-hCys(Trt) and Fmoc-penicillamine(Trt) are used in steps 7 and 1, respectively, instead of Fmoc-Cys(Trt). In addition, in step 9, acetic anhydride is replaced with cyclohexane carboxylic acid, which is pre-activated with DIC (1,3-diisopropylcarbodiimide)/HOBT (1-hydroxybenzotriazole).**

**EXAMPLE 156**

Synthesis of Compound No. 173: N-benzoyl-cyclo [His-D-Phe-Arg-Trp-penicillamine]-NH₂

**[0316] Can be prepared according to Example 1, with the exception that Fmoc-Glu(ObtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. Fmoc-Cys(Trt) and Fmoc-penicillamine(Trt) are used in steps 7 and 1, respectively, instead of Fmoc-Cys(Trt). In addition, in step 9, acetic anhydride is replaced with benzoic acid, which is pre-activated with DIC (1,3-diisopropylcarbodiimide)/HOBT (1-hydroxybenzotriazole).**

**EXAMPLE 157**

Synthesis of Compound No. 174: 4-phenylbutyryl-cyclo[His-D-Phe-Arg-Trp-penicillamine]-NH₂

**[0317] Can be prepared according to Example 1, with the exception that Fmoc-Glu(ObtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. Fmoc-hCys(Trt) and Fmoc-penicillamine(Trt) are used in steps 7 and 1, respectively, instead of Fmoc-Cys(Trt). In addition, in step 9, acetic anhydride is replaced with 4-phenylbutyric acid, which is pre-activated with DIC (1,3-diisopropylcarbodiimide)/HOBT (1-hydroxybenzotriazole).**

**EXAMPLE 158**

Synthesis of Compound No. 175: N-(phenylsulfonfonyl)-cyclo[His-D-Phe-Arg-Trp-penicillamine]-NH₂

**[0318] Can be prepared according to Example 1, with the exception that Fmoc-Glu(ObtBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. In addition, Fmoc-hCys(Trt) and Fmoc-penicillamine(Trt) are used in steps 7 and 1, respectively, instead of Fmoc-Cys(Trt). Acetic anhydride in step 9 is replaced with phenylsulfonylchloride.**

**EXAMPLE 159**

Synthesis of Compound No. 176: (4-benzene-sulfonylamide)butyryl-cyclo[His-D-Phe-Arg-Trp-penicillamine]-NH₂

**[0319] Can be prepared according to Example 1, with the exception that Fmoc-Glu(ObtBu) in step 6 is not used. In step 8, Fmoc-Arg(pbf) is replaced with Fmoc-γ-amino-butryc acid. In addition, Fmoc-hCys(Trt) and Fmoc-penicillamine(Trt) are used in steps 7 and 1, respectively, instead of Fmoc-Cys(Trt). Acetic anhydride in step 9 is replaced with phenylsulfonylchloride.**

**EXAMPLE 160**

Synthesis of Compound No. 177: Ac-nLeu-cyclo [His-D-Phe-Arg-Trp-penicillamine]-NH₂

**[0320] Can be prepared according to Example 1, with the exception that Fmoc-Glu(ObtBu) in step 6 is not used. Fmoc-Cys(Trt) in steps 1 and 7, and Fmoc-Arg(pbf) in step 8, are replaced with Fmoc-penicillamine(Trt), Fmoc-hCys(Trt) and Fmoc-nLeu, respectively.**
EXAMPLE 161

Synthesis of Compound No. 178: N-phenylsulfonyl-Gly-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH₂

[0321] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 is not used. In addition, Fmoc-penicillamine(Trt), Fmoc-Cys(Trt), and Fmoc-Gly are used in steps 1, 7, and 8 instead of Fmoc-Cys(Trt), Fmoc-Cys(Trt), and Fmoc-Arg(pbf), respectively. Acetic anhydride in step 9 is replaced with phenylsulfonylchloride.

EXAMPLE 162

Synthesis of Compound No. 179: cyclo[3-thiopro- pionyl-His-D-Phe-Arg-Trp-hCys]-NH₂

[0322] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6, Fmoc-Arg(pbf) in step 8, and acetylation with acetic anhydride in step 9 are not used. In addition, Fmoc-hCys(Trt) and (S-Trt)-3-thiopro- pionic acid are used instead of Fmoc-Cys(Trt) in steps 1 and 7, respectively.

EXAMPLE 163

Synthesis of Compound No. 180: cyclo[Cys-His-D-Phe-Arg-Trp-hCys]-NH₂

[0323] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) and Fmoc-Arg(pbf) in steps 6 and 8 are not used. Acetylation with acetic anhydride in step 9 is not used. In addition, Fmoc-hCys(Trt) is used instead of Fmoc-Cys(Trt) in step 1.

EXAMPLE 164

Synthesis of Compound No. 181: cyclo[Cys-His-(4- F-D-Phe)-Arg-Trp-hCys]-NH₂

[0324] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6, Fmoc-Arg(pbf) in step 8, and acetylation with acetic anhydride in step 9 are not used. In addition, Fmoc-hCys(Trt) and Fmoc-(4-F-D-Phe) are used instead of Fmoc-Cys(Trt) in step 1 and Fmoc-D-Phe in step 4, respectively.

EXAMPLE 165

Synthesis of Compound No. 182: cyclo[Cys-His-(4- Cl-D-Phe)-Arg-Trp-hCys]-NH₂

[0325] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) and Fmoc-Arg(pbf) in steps 6 and 8 are not used. Acetylation with acetic anhydride in step 9 is not used. In addition, Fmoc-hCys(Trt) and Fmoc-4-Cl-D-Phe are used instead of Fmoc-Cys(Trt) and Fmoc-D-Phe, respectively, in steps 1 and 4.

EXAMPLE 166

Synthesis of Compound No. 183: Ac-cyclo[Cys- His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH₂

[0326] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) and Fmoc-Arg(pbf) in steps 6 and 8 are not used. In addition, Fmoc-hCys(Trt) and Fmoc-4-Cl-D-Phe are used instead of Fmoc-Cys(Trt) and Fmoc-D-Phe, respectively, in steps 1 and 4.

EXAMPLE 167

Synthesis of Compound No. 184: Ac-cyclo[Cys- His-(4-F-D-Phe)-Arg-Trp-hCys]-NH₂

[0327] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. In addition, Fmoc-hCys(Trt) and Fmoc-4-F-D-Phe are used instead of Fmoc-Cys(Trt) in step 1 and Fmoc-D-Phe in step 4, respectively.

EXAMPLE 168

Synthesis of Compound No. 185: Ac-cyclo[Cys- His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH₂

[0328] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and Fmoc-Arg(pbf) in step 8 are not used. In addition, Fmoc-hCys(Trt) and Fmoc-4-Cl-D-Phe are used instead of Fmoc-Cys(Trt) in step 1 and Fmoc-D-Phe in step 4, respectively.

EXAMPLE 169

Synthesis of Compound No. 186: Arg-cyclo[Cys- His-D-Phe-Arg-Trp-hCys]-NH₂

[0329] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and acetylation with acetic anhydride in step 9 are not used. In addition, Fmoc-hCys(Trt) is used instead of Fmoc-Cys(Trt) in step 1.

EXAMPLE 170

Synthesis of Compound No. 187: Arg-cyclo[Cys- His-(4-F-D-Phe)-Arg-Trp-hCys]-NH₂

[0330] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and acetylation with acetic anhydride in step 9 are not used. In addition, Fmoc-hCys(Trt) and Fmoc-(4-F-D-Phe) are used instead of Fmoc-Cys(Trt) in step 1 and Fmoc-D-Phe in step 4, respectively.

EXAMPLE 171

Synthesis of Compound No. 188: Arg-cyclo[Cys- His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH₂

[0331] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and acetylation with acetic anhydride in step 9 are not used. In addition, Fmoc-hCys(Trt) and Fmoc-(4-Cl-D-Phe) are used instead of Fmoc-Cys(Trt) and Fmoc-D-Phe, respectively, in steps 1 and 4.

EXAMPLE 172

Synthesis of Compound No. 189: Ac-Arg-cyclo- [Cys-His-D-Phe-Arg-Trp-hCys]-NH₂

[0332] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 is not used. In addition, Fmoc-hCys(Trt) is used instead of Fmoc-Cys(Trt) in step 1.
EXAMPLE 173

Synthesis of Compound No. 190: Ac-Arg-cyclo
[Cys-His-(4-F-D-Phe)-Arg-Trp-hCys]-NH₂

[0333] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 is not used. In addition, Fmoc-hCys(Trt) and Fmoc-4-F-D-Phe are used instead of Fmoc-Cys(Trt) in step 1 and Fmoc-D-Phe in step 4, respectively.

EXAMPLE 174

Synthesis of Compound No. 191: Ac-Arg-cyclo
[Cys-His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH₂

[0334] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 is not used. In addition, Fmoc-hCys(Trt) and Fmoc-4-Cl-D-Phe are used instead of Fmoc-Cys(Trt) in step 1 and Fmoc-D-Phe in step 4, respectively.

EXAMPLE 175

Synthesis of Compound No. 192: Ac-Tyr-Arg-cyclo
[Cys-Glu-His-D-Phe-Ag-Trp-hCys]-NH₂

[0335] Can be prepared according to Example 1, with the exception that Fmoc-hCys(Trt) is used instead of Fmoc-Cys(Trt) in step 1. Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 176

Synthesis of Compound No. 193: Ac-cyclo[hCys-His-D-Phe-Ag-Trp-hCys]-NH₂

[0336] Can be prepared according to Example 1, with the exception that Fmoc-hCys(Trt) is used instead of Fmoc-Cys(Trt) in steps 1 and 7. Fmoc-Glu(OrBu) is not used in step 6. Fmoc-Ag(Phb) is not used in step 8.

EXAMPLE 177

Synthesis of Compound No. 194: Arg-cyclo[hCys-His-D-Phe-Ag-Trp-hCys]-NH₂

[0337] Can be prepared according to Example 1, with the exception that Fmoc-hCys(Trt) is used instead of Fmoc-Cys(Trt) in steps 1 and 7. Fmoc-Glu(OrBu) is not used in step 6. Acetylation with acetic anhydride in step 9 is not used.

EXAMPLE 178

Synthesis of Compound No. 195: Ac-Arg-cyclo
[hCys-His-D-Phe-Ag-Trp-hCys]-NH₂

[0338] Can be prepared according to Example 1, with the exception that Fmoc-hCys(Trt) is used instead of Fmoc-Cys(Trt) in steps 1 and 7. Fmoc-Glu(OrBu) is not used in step 6.

EXAMPLE 179

Synthesis of Compound No. 196: Ac-Tyr-Arg-cyclo
[hCys-His-D-Phe-Ag-Trp-hCys]-NH₂

[0339] Can be prepared according to Example 1, with the exception that Fmoc-hCys(Trt) is used instead of Fmoc-Cys(Trt) in steps 1 and 7. Fmoc-Glu(OrBu) is not used in step 6. Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 180

Synthesis of Compound No. 197: Ac-Tyr-Arg-cyclo
[hCys-Glu-His-D-Phe-Ag-Trp-hCys]-NH₂

[0340] Can be prepared according to Example 1, with the exception that Fmoc-hCys(Trt) is used instead of Fmoc-Cys(Trt) in steps 1 and 7. Fmoc-Tyr(tBu) is added between steps 8 and 9.

EXAMPLE 181

Synthesis of Compound No. 198: Ac-cyclo(s-CH₂)-S[hCys-His-D-Phe-Ag-Trp-Cys]-NH₂

[0341] Can be prepared according to Example 1, with the exception that Fmoc-Glu(OrBu) in step 6 and Fmoc-Ag(Phb) in step 8 are not used. In addition, after the cleavage and deprotection of the linear peptide from the resin, the cyclization to form the disulfide bond is not carried out. Instead, the crude peptide (200 mg) is suspended in 200 mL of dichloromethane/acetone (1:1 v/v) containing 3 mL of 1.0 M TBAF (tetraethyl ammonium fluoride in THF) and stirring at room temperature for 30 min. Then, 3 mL of glacial acetic acid is added to quench the reaction. The solvents are removed under vacuum.

EXAMPLE 182

Synthesis of Compound No. 198: Ac-cyclo(s-CH₂)-S[hCys-His-D-Phe-Ag-Trp-Cys]-NH₂

[0342] The side-chain protection scheme of amino acids is consistent with standard tert-butyloxycarbonyl Boc chemistry, as shown in Scheme B below: Cys(4-MeBzl), Trp(CH₃), 4-F-D-Phe, His(3-bom), Glu(O-tBu), Cys(4-MeBzl), Arg(p-Tos), Tyr(2-BrZ). Commercially available MBHA resin (Midwest Biotech) is utilized as the solid support. The couplings are carried out either manually by single coupling each residue with a three-fold excess of amino acid activated with DCC/HOBt or by automated methods using an ABI 431A or ABI 433A synthesizer programmed with the manufacturer’s standard t-Boc protocol. N-terminal acetylation is accomplished with 5 equivalents acetic anhydride, 10 equivalents DIEA in dry DMF, 1 hour at room temperature. The triptophan formyl group is deprotected by treatment of the resin-bound peptide with 20% piperidine in DMF, followed by washing with DMF and dichloromethane. The peptides are simultaneously cleaved from the resin and deprotected by treatment with liquid hydrogen fluoride at 0°C for 1 hour in the presence m-cresol and thiocresol scavengers. The peptides are recovered by ether precipitation, washed with ether, extracted into aqueous acetic acid, and lyophilized.

Cyclization Protocol

[0343] The oxidation of the free cysteine sulphydryl groups is accomplished either by air oxidation in 0.2 M ammonium acetate buffer containing 20% dimethyl sulfoxide (DMSO) at pH 7.0, or by treatment with 2,2′-pyridyl disulfide in 2.7 M guanidine buffer containing 30% DMSO. In each case, the final product is isolated by high performance liquid chromatography.
Purification
[0344] Purification is accomplished using standard preparative HPLC techniques. Immediately following the cyclization, the peptide is diluted and loaded onto an HPLC column and eluted with an aqueous 0.1% trifluoroacetic acid/acetonitrile gradient while monitoring at 214 nm. The appropriate fractions are pooled and lyophilized. Further characterization of the final product is performed using analytical HPLC and mass spectral analysis.

Conversion to Acetate Salt
[0345] The peptide is by adsorbed onto a 2.1×25 cm Zorbax C18 preparative column, which is equilibrated with 0.1% TFA/H₂O. The column is then washed with 2 volumes of 0.1 M ammonium acetate/5% acetonitrile followed by 2 column volumes of water. The peptide is eluted using 2% acetic acid and lyophilized.
[0346] The product is characterized using mass spectrometry and HPLC purity detected using acceptable methods in the art and is summarized in Table 2 below.

[0347] Can be prepared according to Example 182, with the exception that Boc-5-Me-(D/L)-His(3-Boc) is used in step 5 instead of Boc-His(3-Bom). The two peptide-isomers are easily separated on HPLC, which affords:

- [0348] Ac-Tyr-Arg-cyclo[Cys-Glu-(5-Me-His)-D-Phe-Arg-Trp-Cys]-NH₂
- Ac-Tyr-Arg-cyclo[Cys-Glu-(5-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH₂

[0349] The absolute configurations of the 5-Me-His residue in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXAMPLE 184

Synthesis of Compound No. 102: Ac-Tyr-Arg-cyclo[Cys-Glu-(1-pyrrozoyl)-Ala]-D-Phe-Arg-Trp-Cys]-NH₂ and Synthesis of Ac-Tyr-Arg-cyclo[Cys-Glu-(1-pyrrozoyl)-D-Ala]-D-Phe-Arg-Trp-Cys]-NH₂

[0350] Can be prepared according to Example 182, with the exception that Boc-1-Pyrrozoyl-(D/L)-Ala is used in step 5 instead of Boc-His(3-Bom). The two peptide-isomers are easily separated on HPLC, which affords:

- [0351] Ac-Tyr-Arg-cyclo[Cys-Glu-(1-pyrrozoyl)-D-Ala]-D-Phe-Arg-Trp-Cys]-NH₂
- Ac-Tyr-Arg-cyclo[Cys-Glu-(1-pyrrozoyl)-D-Ala]-D-Phe-Arg-Trp-Cys]-NH₂

[0352] The absolute configurations of this His residue replacement in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXAMPLE 185


[0353] Can be prepared according to Example 182, with the exception that Boc-4-phenyl-1H-imidazoloyl-(D/L)-Ala is used in step 5 instead of Boc-His(3-Bom). The two peptide-isomers are easily separated on HPLC, which affords:

- [0354] Ac-Tyr-Arg-cyclo[Cys-Glu-(4-phenyl-1H-imidazol-2-yl-D-Ala)]-D-Phe-Arg-Trp-Cys]-NH₂
- Ac-Tyr-Arg-cyclo[Cys-Glu-(4-phenyl-1H-imidazol-2-yl-Ala)]-D-Phe-Arg-Trp-Cys]-NH₂

[0355] The absolute configurations of this His residue replacement in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXAMPLE 186


[0356] Can be prepared according to Example 182, with the exception that Boc-2-Pyrazine-(D/L)-Ala is used in step 5 instead of Boc-His(3-Bom). The two peptide-isomers are easily separated on HPLC, which affords:

- [0357] Ac-Tyr-Arg-cyclo[Cys-Glu-(2-pyrazine-D-Ala)]-D-Phe-Arg-Trp-Cys]-NH₂
- Ac-Tyr-Arg-cyclo[Cys-Glu-(2-pyrazine-Ala)]-D-Phe-Arg-Trp-Cys]-NH₂

[0358] The absolute configurations of this His residue replacement in each peptide are defined by two-dimensional NMR techniques with proper standard peptides and controls.

EXAMPLE 187

Synthesis of Compound No. 106: Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(1,2,4-triazol-3-yl)-Ala)]-D-Phe-Arg-Trp-Cys]-NH₂ and Synthesis of Compound No. 107: Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(1,2,4-triazol-3-yl)-D-Ala)]-D-Phe-Arg-Trp-Cys]-NH₂. Synthesis of Compound No. 108: Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(1-benzyl)-1,2,4-triazol-3-yl)-Ala)]-D-Phe-Arg-Trp-Cys]-NH₂ and Synthesis of Compound No. 109: Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(1-benzyl)-1,2,4-triazol-3-yl)-D-Ala]-D-Phe-Arg-Trp-Cys]-NH₂.

[0359] Can be prepared according to Example 182, with the exception that Boc-(β-(1-benzyl)-1,2,4-triazol-3-yl)-(D/L)-Ala is used in step 5 instead of Boc-His(3-Bom). During HF cleavage, the benzyl protecting-group is partially removed, and the synthesis yields four peptide-isomers. The four peptide-isomers are easily prepared on HPLC, which affords:

- [0360] Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(1-benzyl)-1,2,4-triazol-3-yl)-Ala]-D-Phe-Arg-Trp-Cys]-NH₂
- Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(1,2,4-triazol-3-yl)-D-Ala)]-D-Phe-Arg-Trp-Cys]-NH₂
- Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(1-benzyl)-1,2,4-triazol-3-yl)-Ala]-D-Phe-Arg-Trp-Cys]-NH₂
- Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(1,2,4-triazol-3-yl)-D-Ala)]-D-Phe-Arg-Trp-Cys]-NH₂

[0361] The absolute configurations of this histidine residue replacement in each peptide are defined by two-dimensional NMR techniques with proper peptide standards and controls.

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**EXAMPLE 188**

Construction of MC Receptor Expression Plasmids

**[0362]** Construction of human MC1 expression plasmid: Human MC1 cDNA is cloned by PCR using human genomic DNA (Clontech Cat. # 6550-1) as a template. A forward hMC1 gene-specific primer containing initiation codon (ATG) and EcoRI site and a reverse hMC1 gene specific primer containing a stop codon and XbaI site are used in the PCR. The full-length hMC1 cDNA generated by PCR is cloned into pUC18/Smal plasmid (Pharmacia Cat. # 27-5266-01), and the correct hMC1 cDNA is confirmed by DNA sequencing. The sequenced pUC18hMC1 is digested with EcoRI and XbaI, and the hMC1 cDNA fragment is then subcloned into pCDNA3.1 (Invitrogen Cat. # V790-20) to generate expression plasmid pCDNA3-hMC1.

**[0363]** Construction of human MC3 expression plasmid: Human MC3 cDNA is cloned by PCR using human genomic DNA (Clontech Cat. # 6550-1) as a template. A forward hMC3 gene-specific primer containing initiation codon (ATG) and EcoRI site and a reverse hMC3 gene specific primer containing a stop codon and XbaI site are used in the PCR. The full-length hMC3 cDNA generated by PCR is cloned into pUC18/Smal plasmid (Pharmacia Cat# 27-5266-01), and the correct hMC3 cDNA is confirmed by DNA sequencing. The sequenced pUC18hMC3 is digested with EcoRI and XbaI, and the hMC3 cDNA fragment is then subcloned into pCDNA3.1 (Invitrogen Cat. # V790-20) to generate expression plasmid pCDNA3-hMC3.

**[0364]** Construction of human MC4 expression plasmid: Human MC4 (hMC4) cDNA is cloned in a similar way as hMC3 cDNA by PCR using human fetal brain cDNA- (Clontech Cat. # 7402-1) as a template. The hMC4 cDNA PCR product is digested with EcoRI/XbaI, and then subcloned into pCIneo (Promega Cat. # E1841) and sequenced. The resulting hMC4R plasmid has two mutations, which are then corrected to create the hMC4 cDNA encoding the correct hMC4 protein. The corrected hMC4 cDNA is then subcloned into pCDNA3.1 to generate expression plasmid pCDNA3-hMC4.

**[0365]** Construction of human MC5 expression plasmid: Human MC5 cDNA is cloned by PCR using human genomic DNA (Clontech Cat. # 6550-1) as a template. A forward hMC5 gene-specific primer containing initiation codon (ATG) and HindIII site and a reverse hMC5 gene specific primer containing a stop codon and XbaI site are used in the PCR. The full-length hMC5 cDNA generated by PCR is cloned into pUC18/Smal plasmid (Pharmacia Cat. # 27-5266-01), and the correct hMC5 cDNA is confirmed by DNA sequencing. The sequenced pUC18hMC5 is digested with EcoRI and XbaI, and the hMC5 cDNA fragment is then subcloned into pCDNA3.1 (Invitrogen Cat. # V790-20) to generate expression plasmid pCDNA3-hMC5.

**[0366]** Stable HEK-293 cells expressing human MCs: Stable 293 cells expressing all hMCs are generated by co-transfecting HEK-293 cells with pCDNA3-hMC4R and a CRE-luciferase reporter plasmid following the protocol of Lipofectamine Plus Reagent (Invitrogen, Cat. # 10964-013). For selection of stable transfecants, the Genticin (G418) is added to the media at a concentration of 300 μg/mL 48 hours after the start of transfection. After 2-3 weeks, 40-50 of isolated clones are selected, propagated, and assayed for luciferase activity using a Luciferase Reporter Gene Assay kit (Roche, Cat. # 1814036). Around five stable clones with highly stimulated luciferase activities by 10 nM NDP-αMSH are established.

**EXAMPLE 189**

Melanocortin Receptor Whole Cell cAMP Accumulation Assay

**[0367]** Hank’s Balanced Salt Solution without phenol red (HBSS-092), 1 M HEPES, Dulbecco’s Modified Eagle Media (DMEM), Fetal Bovine Serum (FBS), Antibiotic/ Antimycotic Solution, and sodium acetate are obtained from GibcoBRL. Triton X-100, ascorbic acid, cAMP, and 3-isobutyl-1-methyl-xanthine (IBMX) are purchased from Sigma. Bovine Serum Albumin (BSA) is obtained from Roche. SPA PVT antibody-binding beads type II anti-sheep beads and 125I cAMP are obtained from Amersham. Antigot cAMP antibody is obtained from ICN. Enzyme Free Cell Dissociation Solution Hank’s based is obtained from Specialty Media. NDP-αMSH is obtained from Calbiochem. Dimethylsulfoxide (DMSO) is obtained from Aldrich.
Compound Preparation

In the agonist assay, compounds are prepared as 10 mM and NDP-AMSH (control) as 33.3 μM stock solutions in 100% DMSO. These solutions are serially diluted in 100% DMSO. The compound plate is further diluted in compound dilution buffer (HBSS-092, 1 mM Ascorbic Acid, 1 mM IBMX, 0.6% DMSO, 0.1% BSA) to yield a final concentration range in the assay between 600 nM-6 PM for compound and 100 nM-1 pM for NDP-αMSH control in 0.5% DMSO. Twenty μL of compound solution are transferred from this plate into four PET 96-well plates (all assays are performed in duplicate for each receptor).

Cell Culture and Cell Stimulation

HEK 293 cells stably transfected with the human MC3R or MC4R are grown in DMEM containing 10% FBS and 1% Antibiotic/Antimycotic Solution. On the day of the assay, the cells are dislodged with enzyme free cell dissociation solution and re-suspended in cell buffer (HBSS-092, 0.1% BSA, 10 mM HEPES) at 1x10⁶ cells/mL. Forty μL of cell suspension are added per well to PET 96-well plates containing 20 μL of diluted compound or control. Plates are incubated at 37°C in a waterbath for 20 minutes. The assay is stopped by adding 50 μL Quench Buffer (50 mM sodium acetate, 0.25% Triton X-100).

Determination of cAMP Concentrations

Radioligand binding assays are run in SPA buffer (50 mM sodium acetate, 0.1% BSA). The beads, antibody, and radioligand are diluted in SPA buffer to provide sufficient volume for each 96-well plate. To each quenched assay well is added 100 μL cocktail containing 33.33 μL of beads, 33.33 μL antibody, and 33.33 μL [125I]-cAMP. This is based on a final concentration of 6.3 mg/mL beads, 0.65% anti-goat antibody, and 61 pM of [125I]-cAMP (containing 25,000-30,000 CPM) in a final assay volume of 210 μL. The plates are counted in a Wallac MicroBeta counter after a 12-hour incubation.

The data are converted to pmol of cAMP using a standard curve assay under the same conditions. The data are analyzed using Activity Base software to generate agonist potencies (EC50), and percent relative efficacy data compared to NDP-αMSH.

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**SEQ ID NO 19**

- TYPE: PRT
- ORGANISM: Artificial

**SEQUENCE:**

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<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 30
Cys Glu His Phe Arg Trp Cys
  1  5

<210> SEQ ID NO 31
<211> LENGTH: 7
<212> Type: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1)..(7)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: 4-fluoro substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 31
Cys Glu His Phe Arg Trp Cys
  1  5

<210> SEQ ID NO 32
<211> LENGTH: 7
<212> Type: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1)..(7)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: 4-chloro substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 32
Cys Glu His Phe Arg Trp Cys
  1  5

<210> SEQ ID NO 33
Cys Glu His Phe Arg Trp Cys

1       5

Cys Glu His Phe Arg Trp Cys

1       5

Cys Glu His Phe Arg Trp Cys

1       5
<210> SEQ ID NO 36
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9) . . (9)
<223> OTHER INFORMATION: AMIDATION

Cys Glu His Phe Arg Trp Cys Lys Pro
1  5

<210> SEQ ID NO 37
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7) . . (7)
<223> OTHER INFORMATION: AMIDATION

Cys Glu His Phe Arg Trp Cys Ser Pro
1  5

<210> SEQ ID NO 38
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) . . (1)
<223> OTHER INFORMATION: AMIDATION
-continued

OTHER INFORMATION: N-butyryl substituted
FEATURE:
NAME/KEY: DISULFID
LOCATION: (1) .. (7)
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (4) .. (4)
OTHER INFORMATION: D form
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (7) .. (7)
OTHER INFORMATION: AMIDATION

SEQUENCE: 38
Cys Glu His Phe Arg Trp Cys
1  5

SEQ ID NO 39
LENGTH: 7
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (1) .. (1)
OTHER INFORMATION: N-valeryl substituted
FEATURE:
NAME/KEY: DISULFID
LOCATION: (1) .. (7)
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (4) .. (4)
OTHER INFORMATION: D form
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (7) .. (7)
OTHER INFORMATION: AMIDATION

SEQUENCE: 39
Cys Glu His Phe Arg Trp Cys
1  5

SEQ ID NO 40
LENGTH: 7
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (1) .. (1)
OTHER INFORMATION: 3-quanidinopropionyl substituted
FEATURE:
NAME/KEY: DISULFID
LOCATION: (1) .. (7)
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (4) .. (4)
OTHER INFORMATION: D form
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (7) .. (7)
OTHER INFORMATION: AMIDATION

SEQUENCE: 40
Cys Glu His Phe Arg Trp Cys
1  5

SEQ ID NO 41

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<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: 4-guanidinobutyryl substituted
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1)...(7)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: AMIDATION

SEQ ID NO 41

Cys Glu His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 42
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: 5-guanidinovaleryl substituted
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1)...(7)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)...(4)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: AMIDATION

SEQ ID NO 43

Cys Glu His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 43
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: acetyl-diaminopropionyl substituted
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1)...(7)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)...(4)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: AMIDATION
Cys Glu His Phe Arg Trp Cys

1 5

SEQ ID NO 44
LENGTH:  7
TYPE: PRT
ORGANISM: Artificial
FEATURE: Synthetic construct
OTHER INFORMATION: acetyl-diaminobutyrly substituted
NAME/KEY: MOD_RES
LOCATION: (1)...(1)

SEQ ID NO 45
LENGTH:  8
TYPE: PRT
ORGANISM: Artificial
FEATURE: Synthetic construct
OTHER INFORMATION: D form
NAME/KEY: MOD_RES
LOCATION: (1)...(1)

SEQ ID NO 46
LENGTH:  8
TYPE: PRT
ORGANISM: Artificial
FEATURE: Synthetic construct
OTHER INFORMATION: D form
NAME/KEY: MOD_RES
LOCATION: (1)...(1)
OTHER INFORMATION: AMIDATION
<400> SEQUENCE: 46
Arg Cys Glu His Phe Arg Trp Cys
    1  5

<210> SEQ ID NO 47
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: ACETYlation
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (2)..(8)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 47
Arg Cys Glu His Phe Arg Trp Cys
    1  5

<210> SEQ ID NO 48
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: ACETYlation
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: ACETYlation
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (2)..(8)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: AMIDATION
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 48
Arg Cys Glu His Phe Arg Trp Cys
    1  5

<210> SEQ ID NO 49
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: ACETYlation
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: ACETYlation
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (2)..(8)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: D form

<400> SEQUENCE: 49
Arg Cys Glu His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 50
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: ACETYLATION

<400> SEQUENCE: 50
Arg Cys Glu His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 51
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: 4-chloro substituted, D form

<400> SEQUENCE: 51
Arg Cys Glu His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 52
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
Arg Cys Glu His Phe Arg Trp Cys
1  5

SEQ ID NO 53
LENGTH: 8
ORGANISM: Artificial
FEATURE: Synthetic construct
FEATURE: MOD_RES
LOCATION: (1) (1)
OTHER INFORMATION: ACETYLATION
FEATURE: D form
LOCATION: (5) (5)
OTHER INFORMATION: DISULFID
LOCATION: (2) (8)
OTHER INFORMATION: AMIDATION

SEQ ID NO 54
LENGTH: 8
ORGANISM: Artificial
FEATURE: Synthetic construct
FEATURE: MOD_RES
LOCATION: (1) (1)
OTHER INFORMATION: ACETYLATION
FEATURE: D form
LOCATION: (5) (5)
OTHER INFORMATION: DISULFID
LOCATION: (2) (8)
OTHER INFORMATION: Xaa = homoarginine
<210> SEQ ID NO 55
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8..8)
<223> OTHER INFORMATION: AMIDATION
<400> SEQUENCE: 54

Xaa Cys Glu His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 56
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1..1)
<223> OTHER INFORMATION: ACETYLACTION
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1..1)
<223> OTHER INFORMATION: Xaa = citrulline
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (2..8)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5..5)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8..8)
<223> OTHER INFORMATION: AMIDATION
<400> SEQUENCE: 55

Xaa Cys Glu His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 56
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1..1)
<223> OTHER INFORMATION: ACETYLACTION
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1..1)
<223> OTHER INFORMATION: Xaa = citrulline
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (2..8)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4..4)
<223> OTHER INFORMATION: 1-methyl substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5..5)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8..8)
<223> OTHER INFORMATION: AMIDATION
<400> SEQUENCE: 56

Xaa Cys Glu His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 57
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFDID
<222> LOCATION: (2)...(8)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 57
Leu Cys Glu His Phe Arg Trp Cys

1 5

<210> SEQ ID NO 58
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFDID
<222> LOCATION: (2)...(8)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 58
Lys Cys Glu His Phe Arg Trp Cys

1 5

<210> SEQ ID NO 59
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = N(epsilon)-isopropyl lysine
<220> FEATURE:
<221> NAME/KEY: DISULFDID
<222> LOCATION: (2)...(8)
<210> SEQ ID NO 60
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5) .. (5)
<223> OTHER INFORMATION: D form
</220>
<210> SEQ ID NO 61
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8) .. (8)
<223> OTHER INFORMATION: AMIDATION
</220>

Xaa Cys Glu His Phe Arg Trp Cys

Sequence 1

Xaa Cys Glu His Phe Arg Trp Cys

Sequence 2

Xaa Cys Glu His Phe Arg Trp Cys

Sequence 3
<210> SEQ ID NO 62
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: ACETYLLATION
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: Xaa = Ornithine
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (2) (8)
<223> OTHER INFORMATION: AMIDATION
<200> SEQUENCE: 62

Xaa Cys Glu His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 63
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: ACETYLLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (2) (8)
<223> OTHER INFORMATION: AMIDATION
<200> SEQUENCE: 63

Val Cys Glu His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 64
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: N-(2-naphthalenesulfonyl) substituted, D form
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (2) (8)
Arg Cys Glu His Phe Arg Trp Cys

1  5
<220>  FEATURE:
<223>  OTHER INFORMATION: Synthetic construct
<222>  LOCATION: 3..9

<220>  FEATURE:
<221>  NAME/KEY: DISULFID
<222>  LOCATION: 6..6
<223>  OTHER INFORMATION: D form

<220>  FEATURE:
<221>  NAME/KEY: MOD_RES
<222>  LOCATION: 9..9
<223>  OTHER INFORMATION: NH-(CH2)6-NH2 substituted

<220>  FEATURE:
<221>  NAME/KEY: MOD_RES
<222>  LOCATION: 10..10
<223>  OTHER INFORMATION: AMIDATION

<210> SEQ ID NO 71
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial

Tyr Arg Cys Glu His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 72
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial

Tyr Arg Cys Glu His Phe Arg Trp Cys Glu
1 5 10

<210> SEQ ID NO 73
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial

Tyr Arg Cys Glu His Phe Arg Trp Cys
1 5
SEQ ID NO 74
LENGTH: 9
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
NAME/KEY: MOD_RES
LOCATION: (1) (1)
OTHER INFORMATION: ACETYLATION
NAME/KEY: DISULFID
LOCATION: (3) (3)
NAME/KEY: MOD_RES
LOCATION: (6) (6)
OTHER INFORMATION: D form
AMIDATION

SEQUENCE: 73
Tyr Arg Cys Glu His Phe Arg Trp Cys
1 5

SEQ ID NO 75
LENGTH: 9
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
NAME/KEY: MOD_RES
LOCATION: (1) (1)
OTHER INFORMATION: N-succinyl substituted
NAME/KEY: DISULFID
LOCATION: (3) (3)
NAME/KEY: MOD_RES
LOCATION: (6) (6)
OTHER INFORMATION: D form
AMIDATION

SEQUENCE: 74
Tyr Arg Cys Glu His Phe Arg Trp Cys
1 5

SEQ ID NO 75
LENGTH: 9
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
NAME/KEY: MOD_RES
LOCATION: (1) (1)
OTHER INFORMATION: N-glutaryl substituted
NAME/KEY: DISULFID
LOCATION: (3) (3)
NAME/KEY: MOD_RES
LOCATION: (6) (6)
OTHER INFORMATION: D form
AMIDATION

SEQUENCE: 75
Tyr Arg Cys Glu His Phe Arg Trp Cys
1 5
SEQ ID NO: 76
LENGTH: 9
TYPE: PRT
ORGANISM: Artificial
FEATURE: 
OTHER INFORMATION: Synthetic construct
FEATURE: 
NAME/KEY: MOD_RES
LOCATION: (1)...(1)
OTHER INFORMATION: N-glutaryl substituted
FEATURE: 
NAME/KEY: DISULPFD
LOCATION: (3)...(9)
FEATURE: 
NAME/KEY: MOD_RES
LOCATION: (6)...(6)
OTHER INFORMATION: D form
SEQUENCE: 76

Tyr Arg Cys Glu His Phe Arg Trp Cys
1 5

SEQ ID NO: 77
LENGTH: 9
TYPE: PRT
ORGANISM: Artificial
FEATURE: 
OTHER INFORMATION: Synthetic construct
FEATURE: 
NAME/KEY: MOD_RES
LOCATION: (1)...(1)
OTHER INFORMATION: gluconoyl substituted
FEATURE: 
NAME/KEY: DISULPFD
LOCATION: (3)...(9)
FEATURE: 
NAME/KEY: MOD_RES
LOCATION: (6)...(6)
OTHER INFORMATION: D form
FEATURE: 
NAME/KEY: MOD_RES
LOCATION: (9)...(9)
OTHER INFORMATION: AMIDATION
SEQUENCE: 77

Tyr Arg Cys Glu His Phe Arg Trp Cys
1 5

SEQ ID NO: 78
LENGTH: 9
TYPE: PRT
ORGANISM: Artificial
FEATURE: 
OTHER INFORMATION: Synthetic construct
FEATURE: 
NAME/KEY: MOD_RES
LOCATION: (1)...(1)
OTHER INFORMATION: ACETYLATION
FEATURE: 
NAME/KEY: DISULPFD
LOCATION: (3)...(9)
FEATURE: 
NAME/KEY: MOD_RES
LOCATION: (6)...(6)
OTHER INFORMATION: D form
FEATURE: 
NAME/KEY: MISCE_FEATURE
LOCATION: (9)...(9)
OTHER INFORMATION: Xaa = Cys reduced from amino acid to amino alcohol
SEQUENCE: 78
SEQ ID NO: 79
.getLength: 9
.type: PRT
.organism: Artificial
.feature:

name/key: MOD_RES
.location: (1) (1)

other information: acetylation
.feature:

description: amidation

sequence: Tyr Arg Cys Glu His Phe Arg Trp Xaa

1 5

---continued---
Tyr Arg Cys Glu His Phe Arg Trp Cys

<210> SEQ ID NO 84
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<214> ACETYLATION
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..<1) (1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3)..<9) (9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..<5) (5)
<223> OTHER INFORMATION: 1-methyl substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..<6) (6)
<223> OTHER INFORMATION: 4-fluoro substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)..<9) (9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 84

Tyr Arg Cys Glu His Phe Arg Trp Cys

<210> SEQ ID NO 85
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<214> ACETYLATION
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..<1) (1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3)..<9) (9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..<5) (5)
<223> OTHER INFORMATION: 1-methyl substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..<6) (6)
<223> OTHER INFORMATION: 4-fluoro substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)..<9) (9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 85

Tyr Arg Cys Glu His Phe Arg Trp Cys

<210> SEQ ID NO 86
<211> LENGTH: 9
<212> TYPE: PRT

<210> SEQ ID NO 87
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (1)...(1)
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<222> LOCATION: (3)...(9)
<220> FEATURE:
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<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: 4-chloro substituted, D form
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<222> LOCATION: (2)...(8)
<223> OTHER INFORMATION: 1-methyl substituted
<222> LOCATION: (4)...(4)
<223> OTHER INFORMATION: 1-methyl substituted
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: 4-chloro substituted, D form
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: AMIDATION
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<223> OTHER INFORMATION: AMIDATION
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: AMIDATION
<400> SEQUENCE: 86

Tyr Arg Cys Glu His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 88
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<222> LOCATION: (3)...(9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: 4-chloro substituted, D form
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<222> LOCATION: (2)...(8)
<223> OTHER INFORMATION: 1-methyl substituted
<222> LOCATION: (4)...(4)
<223> OTHER INFORMATION: 1-methyl substituted
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: 4-chloro substituted, D form
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: AMIDATION
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<223> OTHER INFORMATION: AMIDATION
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: AMIDATION
<400> SEQUENCE: 87

Arg Cys Glu His Phe Arg Trp Cys
1  5
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: 4-chloro substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 89

Tyr Arg Cys Glu His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 89
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<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLLATION
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<221> NAME/KEY: DISULPID
<222> LOCATION: (3)...(9)
<223> OTHER INFORMATION: 4-bromo substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: 1-methyl substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 90

Tyr Arg Cys Glu His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 90
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: ACETYLLATION
<220> FEATURE:
<221> NAME/KEY: DISULPID
<222> LOCATION: (3)...(9)
<223> OTHER INFORMATION: 4-bromo substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: AMIDATION
Tyr Arg Cys Glu His Phe Arg Trp Cys
1 5

Tyr Arg Cys Glu His Phe Arg Trp Cys
1 5
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```<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 93
Tyr Arg Cys Glu His Phe Arg Trp Cys
  1  5

<210> SEQ ID NO 94
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLLATION
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)...(9)
<223> OTHER INFORMATION: ACETYLLATION
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: 1-methyl substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: 4-methoxy substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 94
Tyr Arg Cys Glu His Phe Arg Trp Cys
  1  5

<210> SEQ ID NO 95
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLLATION
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)...(9)
<223> OTHER INFORMATION: ACETYLLATION
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: 1-methyl substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: 4-methoxy substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 95
Tyr Arg Cys Glu His Phe Arg Trp Cys
  1  5

<210> SEQ ID NO 96
<211> LENGTH: 9
<212> TYPE: PRT
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<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 96

Tyr Arg Cys Glu His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 97
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 97

Tyr Arg Cys Glu His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 98
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 98

Tyr Arg Cys Glu His Phe Arg Trp Cys
1  5
-continued

<222> LOCATION: (5) ... (5)
<223> OTHER INFORMATION: 5-methyl substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6) ... (6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9) ... (9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 98

Tyr Arg Cys Glu His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 99
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
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<222> LOCATION: (1) ... (1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3) ... (9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5) ... (5)
<223> OTHER INFORMATION: 1-benzyl substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6) ... (6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9) ... (9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 99

Tyr Arg Cys Glu His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 100
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) ... (1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3) ... (9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5) ... (5)
<223> OTHER INFORMATION: 1-benzyl substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6) ... (6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9) ... (9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 100
Tyr Arg Cys Glu His Phe Arg Trp Cys
 1 5

<210> SEQ ID NO 101
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
  <223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
  <221> NAME/KEY: MOD_RES
  <222> LOCATION: (1)...(1)
  <223> OTHER INFORMATION: ACETYLLATION
<220> FEATURE:
  <221> NAME/KEY: DISULFID
  <222> LOCATION: (3)...(9)
<220> FEATURE:
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  <222> LOCATION: (3)...(5)
  <223> OTHER INFORMATION: 1-benzyloxymethyl substituted
<220> FEATURE:
  <221> NAME/KEY: MOD_RES
  <222> LOCATION: (6)...(6)
  <223> OTHER INFORMATION: D form
<220> FEATURE:
  <221> NAME/KEY: MOD_RES
  <222> LOCATION: (9)...(9)
  <223> OTHER INFORMATION: AMIDATION
<400> SEQUENCE: 101
Tyr Arg Cys Glu His Phe Arg Trp Cys
 1 5

<210> SEQ ID NO 102
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
  <223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
  <221> NAME/KEY: MOD_RES
  <222> LOCATION: (1)...(1)
  <223> OTHER INFORMATION: ACETYLLATION
<220> FEATURE:
  <221> NAME/KEY: DISULFID
  <222> LOCATION: (3)...(9)
<220> FEATURE:
  <221> NAME/KEY: MOD_RES
  <222> LOCATION: (6)...(6)
  <223> OTHER INFORMATION: D form
<220> FEATURE:
  <221> NAME/KEY: MOD_RES
  <222> LOCATION: (9)...(9)
  <223> OTHER INFORMATION: AMIDATION
<400> SEQUENCE: 102
Tyr Arg Cys Glu Ala Phe Arg Trp Cys
 1 5

<210> SEQ ID NO 103
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
  <223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
Tyr Arg Cys Glu Ala Phe Arg Trp Cys

1 5

Tyr Arg Cys Glu Ala Phe Arg Trp Cys

1 5
SEQUENCE: 105

Tyr Arg Cys Glu Ala Phe Arg Trp Cys
1 5

SEQUENCE: 106

Tyr Arg Cys Glu Ala Phe Arg Trp Cys
1 5
-continued

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<210> SEQ ID NO 108
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) .. (1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3) .. (9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5) .. (5)
<223> OTHER INFORMATION: beta-((1-benzyl)-1,2,4-triazol-3-yl)
  substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6) .. (6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9) .. (9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 108

Tyr Arg Cys Glu Ala Phe Arg Trp Cys
1  5
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<210> SEQ ID NO 109
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) .. (1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3) .. (9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5) .. (5)
<223> OTHER INFORMATION: beta-((1-benzyl)-1,2,4-triazol-3-yl)
  substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6) .. (6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9) .. (9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 109

Tyr Arg Cys Glu Ala Phe Arg Trp Cys
1  5
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<210> SEQ ID NO 110
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) .. (1)
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<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3) ... (9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5) ... (5)
<223> OTHER INFORMATION: beta-(2-furyl) substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6) ... (6)
<223> OTHER INFORMATION: D form

Tyr Arg Cys Glu Ala Phe Arg Trp Cys
1  5

<210> SEQ ID NO 111
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) ... (1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3) ... (9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5) ... (5)
<223> OTHER INFORMATION: beta-(thien-2-yl) substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6) ... (6)
<223> OTHER INFORMATION: D form

Tyr Arg Cys Glu Ala Phe Arg Trp Cys
1  5

<210> SEQ ID NO 112
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) ... (1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3) ... (9)
<223> OTHER INFORMATION: beta-(1,3-thiazol-4-yl) substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6) ... (6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 112

Tyr Arg Cys Glu Ala Phe Arg Trp Cys
1  5

<210> SEQ ID NO 113
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3)...(9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: beta-(pyridin-4-yl) substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 113

Tyr Arg Cys Glu Ala Phe Arg Trp Cys
1  5

<210> SEQ ID NO 114
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3)...(9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: glycine substituted

<400> SEQUENCE: 114

Tyr Arg Cys Glu His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 115
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
Tyr Arg Cys Glu His Phe Arg Trp Cys
1  5

Tyr Arg Cys Glu His Phe Arg Trp Cys Xaa
1  5  10

Tyr Arg Cys Glu His Phe Arg Trp Cys Xaa
1  5  10
<210> SEQ ID NO 118
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3)...(9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 118

Tyr Arg Cys Glu His Phe Arg Trp Cys Glu
1 5 10

<210> SEQ ID NO 119
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3)...(9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (11)...(11)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 119

Tyr Arg Cys Glu His Phe Arg Trp Cys Ser Pro
1 5 10

<210> SEQ ID NO 120
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3)...(9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
Tyr Arg Cys Glu His Phe Arg Trp Cys Ser Xaa
1  5  10

Tyr Arg Cys Glu His Phe Arg Trp Cys Lys Pro
1  5  10

Tyr Arg Cys Glu His Phe Arg Trp Cys Lys Xaa
1  5  10

Tyr Arg Cys Glu His Phe Arg Trp Cys Lys Pro
1  5  10
Tyr Arg Cys Glu His Phe Arg Trp Cys Arg Phe

Tyr Xaa Cys Glu His Phe Arg Trp Cys

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<210> SEQ ID NO 126
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: D form

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 125
Tyr Xaa Cys Glu His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 127
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: D form

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 126
Tyr Xaa Cys Glu His Phe Arg Trp Cys
1 5
<210> SEQ ID NO: 128
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3)...(9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 128
Tyr Lys Cys Glu His Phe Arg Trp Cys
1  5

<210> SEQ ID NO: 129
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
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<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3)...(9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 129
Tyr Ser Cys Glu His Phe Arg Trp Cys
1  5

<210> SEQ ID NO: 130
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3)...(9)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9) . . (9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 130

Tyr Val Cys Glu His Phe Arg Trp Cys

<210> SEQ ID NO 131
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) . . (1)
<223> OTHER INFORMATION: N-succinyl substituted
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3) . . (9)
<220> FEATURE:
<222> LOCATION: (6) . . (6)
<223> OTHER INFORMATION: D form

<400> SEQUENCE: 131

Tyr Arg Cys Glu His Phe Arg Trp Cys

<210> SEQ ID NO 132
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) . . (6)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1) . . (1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3) . . (3)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6) . . (6)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 132

Xaa His Phe Arg Trp Cys

<210> SEQ ID NO 133
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) . . (6)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1) . . (1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
Xaa His Phe Arg Trp Cys
1 5

SEQ ID NO 134
LENGTH: 6
TYPE: PRT
ORGANISM: Artificial
FEATURE: SYNTHETIC CONSTRUCT
FEATURE: MOD_RES
LOCATION: (3) (3)
OTHER INFORMATION: Xaa = homocysteine

INFORMATION: 4-fluoro substituted, D form
FEATURE: MOD_RES
LOCATION: (3) (3)
OTHER INFORMATION: AMIDATION

INFORMATION: 4-chloro substituted, D form
FEATURE: MOD_RES
LOCATION: (6) (6)
OTHER INFORMATION: ACETYLAION
FEATURE:
<NAME/KEY: DISULFID
LOCATION: (1) . . (6)

FEATURE:
<NAME/KEY: MISC_FEATURE
LOCATION: (1) . . (1)

OTHER INFORMATION: Xaa = homocysteine

FEATURE:
<NAME/KEY: MOD_RES
LOCATION: (6) . . (6)

OTHER INFORMATION: AMIDATION

SEQUENCE: 136
Xaa His Phe Arg Trp Cys
1 5

SEQ ID NO 137
LENGTH: 6
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (1) . . (1)
OTHER INFORMATION: ACETYLATION
FEATURE:
NAME/KEY: DISULFID
LOCATION: (1) . . (6)
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (1) . . (1)
OTHER INFORMATION: Xaa = homocysteine
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (3) . . (3)
OTHER INFORMATION: D form
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (6) . . (6)
OTHER INFORMATION: AMIDATION
SEQUENCE: 137
Xaa His Phe Arg Trp Cys
1 5

SEQ ID NO 138
LENGTH: 6
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (1) . . (1)
OTHER INFORMATION: ACETYLATION
FEATURE:
NAME/KEY: DISULFID
LOCATION: (1) . . (6)
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (1) . . (1)
OTHER INFORMATION: Xaa = homocysteine
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (3) . . (3)
OTHER INFORMATION: D form
SEQUENCE: 138
Xaa His Phe Arg Trp Cys
1 5
<210> SEQ ID NO 139
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1) (6)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3) (3)
<223> OTHER INFORMATION: 4-fluoro substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6) (6)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 139

Xaa His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 140
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1) (6)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3) (3)
<223> OTHER INFORMATION: 4-chloro substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6) (6)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 140

Xaa His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 141
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: N-cyclopropanecarbonyl substituted
Xaa His Phe Arg Trp Cys
1 5

Xaa His Phe Arg Trp Cys
1 5

Xaa His Phe Arg Trp Cys
1 5
Xaa His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 144
<211> LENGTH: 6
<212> TYPE: PRF
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<223> OTHER INFORMATION: N-cyclohexanecarbonyl substituted
<220> FEATURE:
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<223> OTHER INFORMATION: D form
<220> FEATURE:
<223> OTHER INFORMATION: Amidation
<400> SEQUENCE: 144
Xaa His Phe Arg Trp Cys
1 5

Xaa His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 145
<211> LENGTH: 6
<212> TYPE: PRF
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<223> OTHER INFORMATION: N-hexanoyl substituted
<220> FEATURE:
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<223> OTHER INFORMATION: D form
<220> FEATURE:
<223> OTHER INFORMATION: Amidation
<400> SEQUENCE: 145
Xaa His Phe Arg Trp Cys
1 5

Xaa His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 146
<211> LENGTH: 6

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<210> SEQ ID NO 147
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1). . .(1)
<223> OTHER INFORMATION: N-benzoyl substituted
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1). . .(6)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1). . .(1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3). . .(3)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6). . .(6)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 147
Xaa His Phe Arg Trp Cys
1 5

<210> SEQ ID NO 148
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1). . .(1)
<223> OTHER INFORMATION: 3-guanidinopropionyl substituted
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1). . .(6)
<220> FEATURE:
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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = homocysteine

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: D form

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 148

Xaa His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 149
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial

<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: S-guanidinovaleryl substituted

<220> FEATURE:
<221> NAME/KEY: DISULPID
<222> LOCATION: (1)...(6)
<223> OTHER INFORMATION: AMIDATION

<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = homocysteine

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: D form

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 149

Xaa His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 150
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial

<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: N-phenylsulfonyl substituted

<220> FEATURE:
<221> NAME/KEY: DISULPID
<222> LOCATION: (1)...(6)
<223> OTHER INFORMATION: AMIDATION

<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = homocysteine

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: D form

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: AMIDATION
Arg Xaa His Phe Arg Trp Cys

1  5

Arg Xaa His Phe Arg Trp Cys

1  5

Arg Xaa His Phe Arg Trp Cys

1  5
<210> SEQ ID NO 156
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: DISULPID
<222> LOCATION: (2)...(7)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)....(2)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)....(3)
<223> OTHER INFORMATION: 1-methyl substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)....(4)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)....(7)
<223> OTHER INFORMATION: AMIDATION
<400> SEQUENCE: 156

Arg Xaa His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 157
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: DISULPID
<222> LOCATION: (2)...(7)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)....(2)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)....(3)
<223> OTHER INFORMATION: 1-methyl substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)....(4)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)....(7)
<223> OTHER INFORMATION: AMIDATION
<400> SEQUENCE: 157

Arg Xaa His Phe Arg Trp Cys
1  5

<210> SEQ ID NO 158
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)....(1)
OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (2)...(7)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)...(2)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)...(4)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: AMIDATION

SEQUENCE: 158

Arg Xaa His Phe Arg Trp Cys
  1  5

SEQ ID NO 159
LENGTH: 7
TYPE: PRT
ORGANISM: Artificial
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: DISULFID
LOCATION: (2)...(7)
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (2)...(2)
OTHER INFORMATION: Xaa = homocysteine
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (4)...(4)
OTHER INFORMATION: D form

SEQUENCE: 159
Arg Xaa His Phe Arg Trp Cys
  1  5

SEQ ID NO 160
LENGTH: 7
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (1)...(1)
OTHER INFORMATION: ACETYLATION
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (1)...(1)
OTHER INFORMATION: Xaa = norleucine
FEATURE:
NAME/KEY: DISULFID
LOCATION: (2)...(7)
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (2)...(2)
OTHER INFORMATION: Xaa = homocysteine
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (4)...(4)
OTHER INFORMATION: D form
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (7)...(7)
OTHER INFORMATION: AMIDATION

SEQUENCE: 160

Xaa Xaa His Phe Arg Trp Cys
1 5

SEQ ID NO 161
LENGTH: 7
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
NAME/KEY: DISULFID
LOCATION: (2)...(7)
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (2)...(2)
OTHER INFORMATION: Xaa = homocysteine
NAME/KEY: MOD_RES
LOCATION: (4)...(4)
OTHER INFORMATION: D form
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (7)...(7)
OTHER INFORMATION: AMIDATION

SEQUENCE: 161

Gly Xaa His Phe Arg Trp Cys
1 5

SEQ ID NO 162
LENGTH: 8
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
NAME/KEY: DISULFID
LOCATION: (3)...(8)
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (3)...(3)
OTHER INFORMATION: Xaa = homocysteine
NAME/KEY: MOD_RES
LOCATION: (5)...(5)
OTHER INFORMATION: D form
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (8)...(8)
OTHER INFORMATION: AMIDATION

SEQUENCE: 162

Tyr Arg Xaa His Phe Arg Trp Cys
1 5

SEQ ID NO 163
LENGTH: 8
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct

FEATURE:
NAME/KEY: DISULFID
LOCATION: (3) .. (8)

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (3) .. (3)

OTHER INFORMATION: Xaa = homocysteine

FEATURE:
NAME/KEY: MOD_RES
LOCATION: (5) .. (5)

OTHER INFORMATION: D form

SEQUENCE: 163
Tyr Arg Xaa His Phe Arg Trp Cys

SEQ ID NO 164
LENGTH: 8
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (1) .. (1)
OTHER INFORMATION: ACETYLACTION
FEATURE:
NAME/KEY: DISULFID
LOCATION: (3) .. (8)
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (3) .. (3)
OTHER INFORMATION: Xaa = homocysteine
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (5) .. (5)
OTHER INFORMATION: D form
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (8) .. (8)
OTHER INFORMATION: AMIDATION
SEQUENCE: 164
Tyr Arg Xaa His Phe Arg Trp Cys

SEQ ID NO 165
LENGTH: 8
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (1) .. (1)
OTHER INFORMATION: ACETYLACTION
FEATURE:
NAME/KEY: DISULFID
LOCATION: (3) .. (8)
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (3) .. (3)
OTHER INFORMATION: Xaa = homocysteine
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (5) .. (5)
OTHER INFORMATION: D form
SEQUENCE: 165
Tyr Arg Xaa His Phe Arg Trp Cys
-continued

1 5

<210> SEQ ID NO 166
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (3)...(9)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 166

Tyr Arg Xaa Glu His Phe Arg Trp Cys

1 5

<210> SEQ ID NO 167
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1)...(6)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: beta-cyclohexyl substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: AMIDATION

<400> SEQUENCE: 167

Xaa His Ala Arg Trp Cys

1 5

<210> SEQ ID NO 168
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
OTHER INFORMATION: ACETYLATION

NAME/KEY: DISULFID
LOCATION: (1)\ldots(6)

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (1)\ldots(1)

OTHER INFORMATION: Xaa = homocysteine

FEATURE:
NAME/KEY: MOD_RES
LOCATION: (3)\ldots(3)

OTHER INFORMATION: D form

FEATURE:
NAME/KEY: MOD_RES
LOCATION: (6)\ldots(6)

OTHER INFORMATION: AMIDATION

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (6)\ldots(6)

OTHER INFORMATION: Xaa = penicillamine

SEQUENCE: 168
Xaa His Phe Arg Tcp Xaa

SEQ ID NO 169
LENGTH: 6
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (1)\ldots(1)
OTHER INFORMATION: ACETYLATION
FEATURE:
NAME/KEY: DISULFID
LOCATION: (1)\ldots(6)
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (1)\ldots(1)
OTHER INFORMATION: Xaa = homocysteine
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (3)\ldots(3)
OTHER INFORMATION: 4-chloro substituted, D form
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (6)\ldots(6)
OTHER INFORMATION: AMIDATION
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (6)\ldots(6)
OTHER INFORMATION: Xaa = penicillamine

SEQUENCE: 169
Xaa His Phe Arg Tcp Xaa

SEQ ID NO 170
LENGTH: 6
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (1)\ldots(1)
OTHER INFORMATION: N-hexanoyl substituted
FEATURE:
NAME/KEY: DISULFID
LOCATION: (1)\ldots(6)
<210> SEQ ID NO 171
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<222> LOCATION: (1)..<(1)
<223> OTHER INFORMATION: N-cyclopentanecarbonyl substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..<(1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..<(3)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..<(6)
<223> OTHER INFORMATION: AMIDATION
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..<(6)
<223> OTHER INFORMATION: Xaa = penicillamine
<400> SEQUENCE: 171

Xaa His Phe Arg Trp Xaa

<210> SEQ ID NO 172
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<222> LOCATION: (1)..<(1)
<223> OTHER INFORMATION: N-cyclohexanecarbonyl substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..<(1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..<(3)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..<(6)
<223> OTHER INFORMATION: AMIDATION
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..<(6)
<223> OTHER INFORMATION: Xaa = penicillamine
<400> SEQUENCE: 172

Xaa His Phe Arg Trp Xaa

<210> SEQ ID NO 173
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<222> LOCATION: (1)..<(1)
<223> OTHER INFORMATION: N-cyclohexanecarbonyl substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..<(1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: AMIDATION
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
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<223> OTHER INFORMATION: Xaa = penicillamine

<400> SEQUENCE: 172

Xaa His Phe Arg Tcr Xaa

1  5

<210> SEQ ID No 173
<211> LENGTH: 6
<212> TYPE: RNT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: N-benzoyl substituted
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1)...(6)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: AMIDATION
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: Xaa = penicillamine

<400> SEQUENCE: 173

Xaa His Phe Arg Tcr Xaa

1  5

<210> SEQ ID No 174
<211> LENGTH: 6
<212> TYPE: RNT
<213> ORGANISM: Artificial
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: 4-phenylbutyryl substituted
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1)...(6)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: D form
<210> SEQ ID NO 175
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1)...(6)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: (4-benzene sulfonamide)butyryl substituted
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
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<220> FEATURE:
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<223> OTHER INFORMATION: D form
<220> FEATURE:
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<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: AMIDATION
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
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<223> OTHER INFORMATION: Xaa = penicillamine

<400> SEQUENCE: 175

Xaa His Phe Arg Trp Xaa
1  5
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<td>1 5</td>
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<td>Other Information</td>
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<td>1 5</td>
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Gly Xaa His Phe Arg Trp Xaa

1 5

Cys His Phe Arg Trp Xaa

1 5
Cys His Phe Arg Trp Xaa

Cys His Phe Arg Trp Xaa

Cys His Phe Arg Trp Xaa
<400> SEQUENCE: 183
Cys His Phe Arg Trp Xaa
1 5

<210> SEQ ID NO 184
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLATION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1)...(6)
<223> OTHER INFORMATION: 4-fluoro substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: AMIDATION
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: Xaa = homocysteine

<400> SEQUENCE: 184
Cys His Phe Arg Trp Xaa
1 5

<210> SEQ ID NO 185
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
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<220> FEATURE:
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<222> LOCATION: (1)...(6)
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: 4-chloro substituted, D form
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<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: AMIDATION
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<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: Xaa = homocysteine

<400> SEQUENCE: 185
Cys His Phe Arg Trp Xaa
1 5

<210> SEQ ID NO 186
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
-continued

<210> SEQ ID NO 187
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<222> LOCATION: (2) .. (7)
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<220> FEATURE:
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<222> LOCATION: (2) .. (7)
<223> OTHER INFORMATION: 4-fluoro substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4) .. (4)
<223> OTHER INFORMATION: Xaa = homocysteine

Arg Cys His Phe Arg Trp Xaa
1  5

<210> SEQ ID NO 188
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<222> LOCATION: (2) .. (7)
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (2) .. (7)
<223> OTHER INFORMATION: 4-chloro substituted, D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4) .. (4)
<223> OTHER INFORMATION: Xaa = homocysteine

Arg Cys His Phe Arg Trp Xaa
1  5
Arg Cys His Phe Arg Trp Xaa
1 5

Arg Cys His Phe Arg Trp Xaa
1 5
OTHER INFORMATION: ACETYLATION

FEATURE:
NAME/KEY: DISULFID
LOCATION: (2)..(7)

FEATURE:
NAME/KEY: MOD.RES
LOCATION: (4)..(4)
OTHER INFORMATION: 4-chloro substituted, D form

FEATURE:
NAME/KEY: MOD.RES
LOCATION: (7)..(7)
OTHER INFORMATION: AMIDATION

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (7)..(7)
OTHER INFORMATION: Xaa = homocysteine

SEQUENCE: 191

Arg Cys His Phe Arg Trp Xaa
1  5

SEQ ID NO 192
LENGTH: 6
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MOD.RES
LOCATION: (1)..(1)
OTHER INFORMATION: ACETYLATION
FEATURE:
NAME/KEY: DISULFID
LOCATION: (3)..(9)
FEATURE:
NAME/KEY: MOD.RES
LOCATION: (6)..(6)
OTHER INFORMATION: D form
FEATURE:
NAME/KEY: MOD.RES
LOCATION: (9)..(9)
OTHER INFORMATION: AMIDATION
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (9)..(9)
OTHER INFORMATION: Xaa = homocysteine

SEQUENCE: 192

Tyr Arg Cys Glu His Phe Arg Trp Xaa
1  5

SEQ ID NO 193
LENGTH: 6
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MOD.RES
LOCATION: (1)..(1)
OTHER INFORMATION: ACETYLATION
FEATURE:
NAME/KEY: DISULFID
LOCATION: (1)..(6)
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (1)..(1)
OTHER INFORMATION: Xaa = homocysteine
FEATURE:
NAME/KEY: MOD.RES
LOCATION: (3)..(3)
OTHER INFORMATION: D form
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (6)...(6)
OTHER INFORMATION: AMIDATION

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (6)...(6)
OTHER INFORMATION: Xaa = homocysteine

SEQUENCE: 193
Xaa His Phe Arg Trp Xaa
1  5

FEATURE:
NAME/KEY: DISULFID
LOCATION: (2)...(7)

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (2)...(2)
OTHER INFORMATION: Xaa = homocysteine

FEATURE:
NAME/KEY: MOD_RES
LOCATION: (4)...(4)
OTHER INFORMATION: D form

FEATURE:
NAME/KEY: MOD_RES
LOCATION: (7)...(7)
OTHER INFORMATION: AMIDATION

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (7)...(7)
OTHER INFORMATION: Xaa = homocysteine

SEQUENCE: 194
Arg Xaa His Phe Arg Trp Xaa
1  5

FEATURE:
NAME/KEY: MOD_RES
LOCATION: (1)...(1)
OTHER INFORMATION: ACETYLATION

FEATURE:
NAME/KEY: DISULFID
LOCATION: (2)...(7)

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (2)...(2)
OTHER INFORMATION: Xaa = homocysteine

FEATURE:
NAME/KEY: MOD_RES
LOCATION: (4)...(4)
OTHER INFORMATION: D form

FEATURE:
NAME/KEY: MOD_RES
LOCATION: (7)...(7)
OTHER INFORMATION: AMIDATION

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (7)...(7)
OTHER INFORMATION: Xaa = homocysteine
<400> SEQUENCE: 195
Arg Xaa His Phe Arg Trp Xaa
1 5

<210> SEQ ID NO 196
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (3)...(8)
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
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<223> OTHER INFORMATION: D form
<220> FEATURE:
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<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: AMIDATION
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: Xaa = homocysteine

<400> SEQUENCE: 196
Tyr Arg Xaa His Phe Arg Trp Xaa
1 5

<210> SEQ ID NO 197
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
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<220> FEATURE:
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<223> OTHER INFORMATION: Xaa = homocysteine
<220> FEATURE:
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<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: D form
<220> FEATURE:
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<222> LOCATION: (9)...(9)
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<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: Xaa = homocysteine

<400> SEQUENCE: 197
Tyr Arg Xaa Glu His Phe Arg Trp Xaa
<210> SEQ ID NO 198
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: ACETYLACTION
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (1)...(6)
<223> OTHER INFORMATION: S-CH2-S linkage
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: D form
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: AMIDATION
<400> SEQUENCE: 198

Cys His Phe Arg Trp Cys

<210> SEQ ID NO 199
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = Arg, Tyr-Arg, Tyr-beta-Arg, or is absent
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = a modified amino acid including Arg, citrulline, homocitrulline, Leu, Lys, N-isopropyl-Lys, norleucine, ornithine, or Val
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: Xaa = a modified group including Tyr-Arg, Tyr-citrulline, Cys-Arg, Tyr-homoarginine, Tyr-l-beta-homocitrulline, Tyr-Lys, Tyr-Ser, or Tyr-Val
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (2)...(8)
<223> OTHER INFORMATION: S-S or S-CH2-S disulfide bridge
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)...(2)
<223> OTHER INFORMATION: Xaa = Cys, homocysteine, or desamino-cysteine; may be D or L form
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: Xaa = Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr, Trp, Phe, Lys, Leu, cysteic acid, or is absent
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)...(4)
<223> OTHER INFORMATION: Xaa = His, modified His, or modified Ala; D or L form
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
Xaa Xaa Xaa Xaa Xaa Xaa Trp Xaa Xaa
1 5

SEQ ID NO: 200
LENGTH: 8
TYPE: PRT
ORGANISM: Artificial

OTHER INFORMATION: Synthetic construct

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (1)...(1)
OTHER INFORMATION: Xaa = Arg, Tyr-Arg, Tyr-beta-Arg, or is absent

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (1)...(1)
OTHER INFORMATION: Xaa = Glu, Gln, Asp, Asn, Ala, Glv, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr, Trp, Phe, Lys, Leu, cysteic acid, or is absent

FEATURE:
NAME/KEY: MOD_RES
LOCATION: (4)...(4)
OTHER INFORMATION: His may be optionally substituted, D or L form

FEATURE:
NAME/KEY: MOD_RES
LOCATION: (5)...(5)
OTHER INFORMATION: Phe may be optionally substituted, D or L form

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (8)...(8)
OTHER INFORMATION: Xaa = Cys, homocysteine, or modified cysteine or homocysteine such as amide

FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (9)...(9)
OTHER INFORMATION: Xaa = Ser-Pro-NH2, Lys-Pro-NH2, Ser-CH2, 
Ser-Pro-CH2, Lys-OH, Ser-alcohol, Ser-Pro-alcohol, Arg-Phe-NH2, 
Glu-NH2, or is absent

SEQUENCE: 200

Xaa Xaa Xaa His Phe Arg Xaa Xaa
1 5

SEQ ID NO: 201
LENGTH: 9
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: Synthetic construct
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (1)(1)
OTHER INFORMATION: Xaa = Arg, Tyr-Arg, Tyr-beta-Arg, or is absent
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (1)(1)
OTHER INFORMATION: Xaa = a modified amino acid including Arg, 
citrulline, homocarnginine, Leu, Lys, N-isopropyl-Lys, norleucine, 
ornithine, or Val
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (1)(1)
OTHER INFORMATION: Xaa = a modified group including Tyr-Arg, 
Tyr-citrulline, Tyr-homocarnginine, Tyr-beta-homocarnginine, 
Tyr-Lys, Tyr-Ser, or Tyr-Val
FEATURE:
NAME/KEY: DISULFID
LOCATION: (2)(8)
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (2)(2)
OTHER INFORMATION: Xaa = Cys or homocysteine
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (3)(3)
OTHER INFORMATION: Xaa = Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, 
Pro, Met, Ile, Val, Arg, His, Tyr, Trp, Phe, or is absent
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (4)(4)
OTHER INFORMATION: His may be optionally substituted, D or L form
FEATURE:
NAME/KEY: MOD_RES
LOCATION: (5)(5)
OTHER INFORMATION: Phe may be optionally substituted, D or L form
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (8)(8)
OTHER INFORMATION: Xaa = Cys, homocysteine, or modified cysteine 
or homocysteine such as amide
FEATURE:
NAME/KEY: MISC_FEATURE
LOCATION: (9)(9)
OTHER INFORMATION: Xaa = Ser-Pro-NH2, Lys-Pro-NH2, Ser-CH2, 
Ser-Pro-CH2, Lys-OH, Ser-alcohol, Ser-Pro-alcohol, Arg-Phe-NH2, Glu-NH2, or is absent

SEQUENCE: 201

Xaa Xaa Xaa His Phe Arg Trp Xaa Xaa
1 5
1. A compound selected from the group consisting of Compound Numbers 1-198.
2. (canceled)
3. The compound of claim 11, wherein the compound is AC-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH$_2$.
4. The compound of claim 11, wherein the compound is Ac-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH$_2$.
5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one compound as claimed by claim 11.
6. A method for agonizing the MC4 receptor, comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of at least one compound of any one as claimed in claim 11.
7. A method of treating obesity in a mammal, comprising the step of administering to the mammal in need thereof a pharmaceutically effective amount of at least one compound of any one as claimed in claim 11.
8. A method of treating diabetes mellitus in a mammal, comprising the step of administering to the mammal in need thereof a pharmaceutically effective amount of at least one compound as claimed in claim 11.
9. A method of treating male and/or female sexual dysfunction in a mammal, comprising the step of administering to the mammal in need thereof a pharmaceutically effective amount of at least one compound as claimed in claim 11.
10. (canceled)
11. (canceled)
12. (canceled)
13. (canceled)
14. (canceled)
15. (canceled)
16. (canceled)
17. (canceled)
18. (canceled)
19. (canceled)
20. (canceled)
21. (canceled)
22. (canceled)
23. (canceled)
24. (canceled)
25. (canceled)
26. (canceled)
27. (canceled)
28. (canceled)